2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,1,1-trichloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt

at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user’s perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for 1,1,1-trichloroethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute-, intermediate-, and chronic-duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User’s Guide has been provided at the end of this profile (see Appendix A). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.l Death

1,1,1-Trichloroethane is one of many solvents intentionally inhaled by some people to alter mood or consciousness. Solvent abuse of this type is associated with “sudden sniffing death” syndrome. In a survey of sudden sniffing deaths across the United States in the 1960s, 29 of the 110 deaths in the survey were attributed to inhalation of 1,1,1-trichloroethane (Bass 1970). Case reports of individuals who died following intentional inhalation of 1,1,1-trichloroethane are readily available (D’Costa and Gunasekera 1990; Droz et al. 1982; Guberan et al. 1976; Hall and Hine 1966; MacDougall et al. 1987; Ranson and Berry 1986; Travers 1974). 1,1,1-Trichloroethane is a widely used industrial solvent. Although mortality due to accidental exposure from its use as a solvent is not common, a number of cases have been reported (Caplan et al. 1976; Jones and Winter 1983; McCarthy and Jones 1983; Mercier 1977; Northfield 1981; Silverstein 1983; Stahl et al. 1969).

Data from case reports and surveys are useful, but concomitant exposure to other chemicals cannot be ruled out, and exposure concentrations and durations are rarely known. Although the actual levels of exposure that produced death are not known for any of these cases, some investigators used simulations to estimate the fatal exposure concentrations. Droz et al. (1982) performed detailed simulations of two fatalities from intentional 1,1,1-trichloroethane inhalation. The lethal concentration of 1,1,1-trichloroethane was estimated to be between 6,000 and 14,000 ppm in one case and between 10,000 and 20,000 ppm in the other. Simulation of the circumstances of deaths of two people exposed while using 1,1,1-trichloroethane as a solvent showed that concentrations 16,400 ppm may have been generated in one case (Jones and Winter 1983), and concentrations 19,000 ppm may have been generated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source.

Human death following acute exposure to high 1,1,1-trichloroethane concentrations is usually attributed to either depression of the central nervous system, which results in respiratory arrest (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969), or sensitization of the heart to epinephrine, which results in severe cardiac arrhythmias (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). The occurrence of death during physical exertion following inhalation of 1,1,1-trichloroethane

(Ranson and Berry 1986) or a mixture of 1,1,1-trichloroethane and trichloroethylene (King et al. 1985; Troutman 1988) is consistent with the possibility that cardiac sensitization to epinephrine caused death in these cases. It should be noted that anoxia or hypoxia, which are present to some extent during physical exertion, exacerbate the cardiac arrhythmias caused by sensitization of the myocardium to catecholamines (Reinhardt et al. 1971).

Studies of animal mortality following acute inhalation exposure to 1,1,1-trichloroethane are numerous. Median lethal concentrations (LC_{50} values) have been calculated for rats and mice. For rats, LC_{50} values from 10,305 to 38,000 ppm were reported (Adams et al. 1950; Bonnet et al. 1980; Clark and Tinston 1982). For mice, reported LC_{50} values ranged from 3,911 to 22,241 ppm (Gradiski et al. 1978; Horiguchi and Horiguchi 1971; Moser and Balster 1985; Woolverton and Balster 1981). Much of the variation in these data can be attributed to differences in the exposure duration (higher LC_{50} values were generally obtained in studies with short exposure periods). In studies of the same duration, rats (6-hour LC_{50} = 10,305 ppm) were somewhat more susceptible to 1,1,1-trichloroethane than mice (6-hour LC_{50} = 13,414 ppm) (Bonnet et al. 1980; Gradiski et al. 1978). An alternative way to study lethality is to expose animals to a given concentration of vapor and record the time required to kill half of the animals (LT_{50}). The LT_{50} was 180 minutes in rats exposed to 18,000 ppm of 1,1,1-trichloroethane (Adams et al. 1950) and 595 minutes in mice exposed to 13,500 ppm (Gehring 1968). Deaths of animals exposed to 1,1,1-trichloroethane were usually attributed to either respiratory or cardiac failure (Adams et al. 1950; Clark and Tinston 1982; Krantz et al. 1959). Most deaths occurred during exposure. Animals that survived the exposure period usually recovered rapidly and appeared normal within 10-15 minutes (Adams et al. 1950; Clark and Tinston 1982).

1,1,1-Trichloroethane did not increase mortality in longer-term studies in which animals were exposed to lower exposure concentrations than the acute studies. No effects on survival were observed in intermediate-duration studies in which animals of several species were exposed to concentrations ≤5,000 ppm (Adams et al. 1950; Calhoun et al. 1981; Prendergast et al. 1967; Rosengren et al. 1985) or chronic-duration studies in which rats and mice were exposed to concentrations ≤1,750 ppm (Quast et al. 1978, 1988).

Reliable acute LC_{50} values for death in each species are recorded in Table 2-l and plotted in Figure 2-l. Acute exposure to high concentrations of 1,1,1-trichloroethane can be lethal to humans and animals. The cause of death is usually either respiratory or cardiac failure. Limited human data

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (Sprague-Dawley)	1 d 6hr/d				10305 M (LC50 - 6 hr)	Bonnet et al. 1980
2	Rat (Alderley-Park)	1 d 10-15 min/d				38000 (LC50 - 15 min)	Clark and Tinston 1982
3	Rat (Wistar)	1 d 6-420 min/d				14250 (LC50 - 7 hr)	Adams et al. 1950
4	Mouse (OF1)	1 d 6hr/d				13414 F (LC50 - 6 hr)	Gradiski et al. 1978
5	Mouse (NA2)	1 d 2hr/d				3911 M (LC50 - 2 hr)	Horiguchi and Horiuchi 1971
6	Mouse (CD-1)	1 d 30 min/d				22241 M (LC50 - 30 min)	Woolverton and Balster 1981
7	Mouse (CD-1)	1 d 10-60 min/d				18358 M (LC50 - 60 min)	Moser and Balster 1985
	Systemic						
8	Human	1 d 30 min/d	Cardio	550 M			Gamberale and Hultengren 1973
9	Human	1 d 15-186 min/d	Resp		1900M (throat irritation)		Stewart et al. 1961
			Hepatic	2650 M			
			Renal	2650 M			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
10	Human	1 d up to 2 hr/d	Resp	10000			Dornette and Jones 1960
			Cardio		10000 (5-10 mm Hg reduction in blood pressure)		
			Hepatic	10000			
11	Human	5 d 1-7.5 hr/d	Resp	500			Stewart et al. 1975
			Hemato	500			
			Hepatic	500			
			Renal	500			
12	Human	1 d 5-450 min/d	Resp	506			Torkelson et al. 1958
			Cardio	920			
			Hemato	920			
			Hepatic	920			
			Renal	920			
13	Rat (NS)	1 d 2 hr/d	Hepatic	13070 M			Carlson 1973
14	Rat (Wistar)	10 d 24 hr/d	Hemato	800 M			Koizumi et al. 1983
			Hepatic	800 M			
15	Rat (Sprague-Dawley)	5 d 6 hr/d	Hepatic	500 M			Savolainen et al. 1977
16	Rat (Sprague-Dawley)	1 d 24hr/d	Hepatic	2500 M			Fuller et al. 1970
17	Rat (Wistar)	1 d 6-420 min/d	Bd Wt	30000			Adams et al. 1950

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
18	Rat (Sprague-Dawley)	1 d 2 hr/d	Resp	15000 M			Comish and Adefuin 1966
			Hepatic	15000 M			
			Renal	15000 M			
			Endocr	15000 M			
			Bd Wt	15000 M			
19	Rat (Wistar)	1 d 6-420 min/d	Resp	18000 M			Adams et al. 1950
			Cardio	18000 M			
			Hepatic		8000M (increased liver weight, mild fatty change)		
			Renal	18000 M			
			Bd Wt	18000 M			
20	Mouse (Swiss Webster)	1 d 10-780 min/d	Hepatic	13500 F			Gehring 1968
21	Mouse (Swiss albino)	1-6 d 4-24 hr/d	Hepatic	6000 M			Lal and Shah 1970
22	Mouse (CFW Swiss)	4 d 24 hr/d	Bd Wt	2000 M		4000 M (26% reduction in body weight)	Evans and Balster 1993
23	Dog (Beagle)	1 d 10 min/d	Cardio	2500 M		5000 M (cardiac sensitization)	Reinhardt et al. 1973
24	Dog (Beagle)	1 d 5 min/d	Cardio			7500 (EC50 for cardiac sensitization)	Clark and Tinston 1973
25	Dog (Beagle)	1 d 15min/d	Cardio	10000			Egle et al. 1976

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
26	Dog (NS)	1 d 5 min/d	Resp	25000			Herd et al. 1974
			Cardio			8000 (50 mm Hg reduction in mean blood pressure)	
			Hepatic	25000			
27	Rabbit (New Zealand)	1 d 7.5-60 min/d	Cardio			5600 M (cardiac sensitization)	Carlson 1981
	Immunological/Lymphoreticular						
28	Rat (Sprague-Dawley)	1 d 2 hr/d		15000 M			Cornish and Adefuin 1966
29	Mouse (CD-1)	1 d 3hr/d		350 F			Aranyi et al. 1986
	Neurological						
30	Human	1 d 30 min/d		250 M	350 M (increased reaction time, decreased perceptual speed and manual dexterity)		Gamberale and Hultengren 1973
31	Human	1 d 3.5 hr/d			175[b] M (decreased psychomotor performance)		Mackay et al. 1987
32	Human	5 d 6.5-7 hr/d				500 M (impaired balance)	Stewart et al. 1969
33	Human	1 d 15-186 min/d		496 M		900 M (lightheadedness)	Stewart et al. 1961
34	Human	1 d up to 2 hr/d				10000 (anesthesia)	Dornette and Jones 1960

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
35	Human	5 d 1-7.5 hr/d		350	500 (altered EEG)		Stewart et al. 1975
36	Human	1 d 5-450 min/d				920 (ataxia)	Torkelson et al. 1958
37	Monkey (Baboon)	1 d 4hr/d		1400 M	1800M (increased response time in match to sample task)		Geller et al. 1982
38	Rat (Sprague-Dawley)	1 d 6hr/d				10000 M (all somnolent)	Bonnet et al. 1980
39	Rat (Alderley Park)	1 d 10-15 min/d				5000 (EC50 for ataxia)	Clark and Tinston 1982
40	Rat (Wistar)	1 d 5-60 min/d			8000M (increased brain lactate and pyruvate)		Folbergrova et al. 1984
41	Rat (Wistar)	1 d 0.5-2 hr/d		3500 M	6000M (dizzness, decrease local cerebral glucose consumption)	7800 M (ataxia)	Hougaard et al. 1984
42	Rat (Charles River-CD)	1 d 0.5-4 hr/d		1750 M		3080 M (impaired reflexes)	Mullin and Krivanek 1982
43	Rat (Wistar)	1 d 6-420 min/ d				5000 (narcosis)	Adams et al. 1950
44	Rat (Fischer 344)	4 d 6 hr/d			1000 F (altered EEG, FEP, and SEP)		Albee et al. 1990b
45	Rat (Fischer 344)	4 d 6 hr/d				4000 (increased motor activity)	Albee et al. 1990a

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
46	Mouse (Swiss Webster)	1 d 10-780 min/d				13500 F (unconsciousness)	Gehring 1968
47	Mouse (NS)	1 d 2 hr/d				7330 (prostration)	Lazarew 1929
48	Mouse (CD-1)	1 d 20 min/d				2876 M (EC50 for effect on ability to discriminate from pentobarbital)	Rees et al. 1987a
49	Mouse (CD-1)	1 d 20 min/d				850 M (EC50 for effect on ability to discriminate from ethanol)	Rees et al. 1987b
50	Mouse (Swiss OF1)	1 d 4 hr/d				6644 M (EC50 for increased seizure threshold)	De Ceaurriz et al. 1981
51	Mouse (NS)	1 d 4 hr/d		50 M	100M (reduced cGMP in brain)		Nilsson 1986b
52	Mouse (NS)	1 d 4 hr/d		500 M	1000M (increased cAMP in brain)		Nilsson 1986a
53	Mouse (NMRI)	1 d 1hr/d		1300 M		2000 M (increased motor activity)	Kjellstrand et al. 1985a
54	Mouse (CD-1)	1 d 20 min/d				2836 M (EC50 for effect on operant behavior)	Balster et al. 1982
55	Mouse (CD-1)	1 d 30 min/d				5173 M (EC50 for impaired screen climbing ability)	Woolverton and Balster 1981
56	Mouse (Swiss OF1)	1 d 4 hr/d				2064 M (altered swimming behavior)	De Ceaurriz et al. 1983

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
57	Mouse (CD-1)	1 d 30 min/d				7129 M (EC50 for reduced fixed interval response rate)	Moser and Balster 1986
58	Mouse (CD-1)	1 d 10-60 min/d				5674 M (EC50 for impaired screen climbing ability)	Moser and Balster 1985
59	Mouse (CFW Swiss)	4 d 24 hr/d				500 M (decreased threshold to convulsions upon withdrawal)	Evans and Balster 1993
60	Dog (Beagle)	1 d 15 min/d		10000			Egle et al. 1976
	Reproductive						
61	Rat (NS)	1 d 6-420 min/d		18000 M			Adams et al. 1950
	Developmental						
62	Rat (Sprague-Dawley)	Gd 6-15 7 hr/d		875 F			Schwetz et al. 1975
63	Rat (CD)	Gd 6-15 4 hr/d		3000 F	6000 F (decreased female fetal weight, delayed ossification)		BRRC 1987a
64	Mouse (Swiss Webster)	Gd 6-15 7 hr/d		875 F			Schwetz et al. 1975
65	Rabbit (New Zealand)	Gd 6-18 6 hr/d		3000 F	6000 F (extra rib)		BRRC 1987b

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
66	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			
67	Monkey (NS)	14 wk 7 d/wk 24 hr/d	Resp	1000			MacEwen and Vernot 1974
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
68	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			
69	Rat (Sprague-Dawley)	4 wk 5 d/wk 6 hr/d	Hepatic	820 M			Toftgard et al. 1981
			Bd Wt	820 M			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
70	Rat (Sprague-Dawley)	15 wk 5 d/wk 5-6 hr/d	Resp	1100 F			Truffert et al. 1977
			Hemato	1100 F			
			Hepatic	1100 F			
			Renal	1100 F			
			Bd Wt	1100 F			
71	Rat (NS)	14 wk 24 hr/d	Resp	1000			MacEwen and Vernot 1974
			Hepatic	1000			
			Renal	1000			
			Bd Wt	1000			
72	Rat (NS)	3 mo 5 d/wk 3-60 min/d	Hepatic	10000 M			Torkelson et al. 1958
			Renal	10000 M			
			Bd Wt	10000 M			
73	Rat (CDF)	90 d 5 d/wk 6 hr/d	Resp	1000	2000	(mild nasal epithelial degeneration)	Calhoun et al. 1981
			Cardio	2000			
			Gastro	2000			
			Hemato	2000			
			Musc/skel	2000			
			Hepatic	1000	2000	(reduced glycogen, fatty change)	
			Renal	2000			
			Derm	2000			
			Ocular	2000			
			Bd Wt	2000			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
74	Rat (NS)	44 d 5 d/wk 7 hr/d	Resp	5000			Adams et al. 1950
			Cardio	5000			
			Hepatic	5000			
			Renal	5000			
			Bd Wt	5000			
75	Mouse (CF1)	14 wk 24 hr/d	Hepatic	250 M	1000M (fatty change, necrosis)		McNutt et al. 1975
76	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d	Resp	1000	2000 (mild nasal epithelial degeneration)		Calhoun et al. 1981
			Cardio	2000			
			Gastro	2000			
			Hemato	2000			
			Musc/skel	2000			
			Hepatic	1000	2000 (fatty change)		
			Renal	2000			
			Derm	2000			
			Ocular	2000			
			Bd Wt	2000			
77	Dog (Beagle)	90 d 24 hr/d	Resp	380			Prendergast et al. 1967
			Cardio	380			
			Hemato	380			
			Hepatic	380			
			Renal	380			
			Bd Wt	140		380 (body weight gain reduced 51%)	

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
78	Dog (Beagle)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt		2210 (body weight gain reduced >12%)		
79	Dog (NS)	14 wk 24 hr/d	Gastro	1000			MacEwen and Vernot 1974
			Hemato	1000			
			Hepatic	1000			
			Renal	1000			
80	Rabbit (New Zealand albino)	90 d 24 hr/d	Resp	380			Prendergast et al. 1967
			Cardio	380			
			Hemato	380			
			Hepatic	380			
			Renal	380			
			Bd Wt	140		380 (66% reduction in body weight gain)	
81	Rabbit (New Zealand albino)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt			2210 (over 34% reduction in body weight gain)	

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
82	Rabbit (NS)	6 mo 5 d/wk 7 hr/d	Resp	500			Torkelson et al. 1958
			Cardio	500			
			Hemato	500			
			Hepatic	500			
			Renal	500			
			Bd Wt	500			
83	Rabbit (NS)	44 d 5 d/wk 7 hr/d	Resp	5000 F			Adams et al. 1950
			Hepatic	5000 F			
			Renal	5000 F			
			Bd Wt		5000 F (slight decrease in body weight gain)		
84	Gerbil (Mongolian)	3 mo 24 hr/d	Bd Wt	1000			Rosengren et al. 1985
85	Gn pig (Hartley)	6 wk 5 d/wk 8 hr/d	Resp	2210			Prendergast et al. 1967
			Cardio	2210			
			Hemato	2210			
			Hepatic	2210			
			Renal	2210			
			Bd Wt	2210			
86	Gn pig (NS)	3 mo 5 d/wk 3-180 min/d	Resp		1000 F (lung irritation)		Torkelson et al. 1958
			Hepatic		1000 F (fatty change)		
			Renal	2000 F			
			Bd Wt	2000 F			

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
87	Gn pig (NS)	45 d 5 d/wk 7 hr/d	Resp	5000					Adams et al. 1950
			Hepatic		5000	(fatty change)			
			Renal	5000					
			Bd Wt				5000	(over 20% decrease body weight gain)	
88	Gn pig (NS)	30 d 7 hr/d	Resp	3000					Adams et al. 1950
			Cardio	3000					
			Hepatic		3000	(fatty change)			
			Renal	3000					
			Bd Wt				3000	(over 20% reduction in body weight gain)	
89	Gn pig (NS)	93 d 5 d/wk 7 hr/d	Resp	650					Adams et al. 1950
			Cardio	650					
			Hepatic	650					
			Renal	650					
			Bd Wt		650	(body weight gain reduced 18-35%)			
Immunological/Lymphoreticular									
90	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d		2210					Prendergast et al. 1967
91	Rat (Sprague-Dawley)	6 wk 5d/wk 8hr/d		2210					Prendergast et al. 1967

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
92	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		2000			Calhoun et al. 1981
93	Dog (Beagle)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
94	Rabbit (NS)	44 d 5 d/wk 7 hr/d		5000 F			Adams et al. 1950
95	Gn pig (NS)	45 d 5 d/wk 7 hr/d		5000			Adams et al. 1950
	Neurological						
96	Monkey (Squirrel)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
97	Rat (Sprague-Dawley)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
98	Rat (NS)	3 mo 5 d/wk 3-60 min/d				10000 M (ataxia, narcosis)	Torkelson et al. 1958
99	Rat (Fischer 344)	13 wk 5 d/wk 6 hr/d		630	2000 (decreased forelimb grip performance)		Mattsson et al. 1993
100	Mouse (CD-1)	4 wk 4 d/wk 20 min/d			3300M (EC50 for decreased response rate)		Moser et al. 1985

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key [a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
101	Dog (Beagle)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
102	Rabbit (New Zealand albino)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
103	Gn pig (Hartley)	6 wk 5 d/wk 8 hr/d		2210			Prendergast et al. 1967
104	Gerbil (Mongolian)	3 mo 24 hr/d			70 (decreased DNA content in some brain areas)		Karlsson et al. 1987
105	Gerbil (Mongolian)	3 mo 24 hr/d		70 [c]		210 (increased GFA protein indicating astrogliosis)	Rosengren et al. 1985
	Reproductive						
106	Rat (NS)	44 d 5 d/wk 7 hr/d		5000 M			Adams et al. 1950
107	Mouse (B6C3F1)	90 d 5 d/wk 6 hr/d		2000			Calhoun et al. 1981
108	Rabbit (NS)	6 mo 5 d/wk 7 hr/d		500 M			Torkelson et al. 1958
109	Gn pig (NS)	45 d 5 d/wk 7 hr/d			5000 M (testicular degeneration)		Adams et al. 1950

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key to figure [a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
110	Gn pig (NS)	30 d 7 hr/d		3000 M			Adams et al. 1950
	Developmental						
111	Rat Long-Evans	premating: 2 wk 5 d/wk 6 hr/d pregnancy: Gd 1-20 7 d/wk 6 hr/d			2100 F (delayed ossification, reduced clavicle)		York et al. 1982
	CHRONIC EXPOSURE						
	Systemic						
112	Human	up to 6 yr (occup)	Cardio	150			Kramer et al. 1978
			Hemato	150			
			Hepatic	150			
			Renal	150			
113	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d	Resp	1500			Quast et al. 1988
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Bd Wt		500 F (body weight reduced up to 8%)		

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
114	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d	Resp	1500			Quast et al. 1988
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Derm	1500			
			Bd Wt	1500			
Immunological/Lymphoreticular							
115	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
116	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
Neurological							
117	Human	6.7 yr avg (occup)		200 F			Maroni et al. 1977
118	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
119	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988

TABLE 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane - Inhalation (continued)

Key[a] to figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
Reproductive							
120	Rat (Fischer 344)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988
121	Mouse (B6C3F1)	2 yr 5 d/wk 6 hr/d		1500			Quast et al. 1988

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 2 ppm; unadjusted exposure concentration divided by an uncertainty factor of 100 (10 for human variability and 10 for use of a LOAEL)
[c]used to derive an intermediate inhalation MRL of 0.7 ppm; continuous exposure concentration divided by an uncertainty factor of 100 (10 for extrapolation from gerbils to humans and 10 for human variability)

avg = average; Bd Wt = body weight; cAMP = cyclic adenosine monophosphate; Cardio = cardiological; cGMP = cyclic guanidine monophosphate; d = day(s); Derm = dermal; DNA = deoxyribonucleic acid; EC_{50} = effective concentration, 50%; EEG = electroencephalogram; Endocr = endocrine; F = female; FEP = flash evoked potential; Gastro = gastrointestinal; Gd = gestation day; GFA = glial fibrillary acid; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NS = not specified; NOAEL = no-observed-adverse-effect level; occup = occupational; resp = respiratory; SEP = somatosensory evoked potential; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation

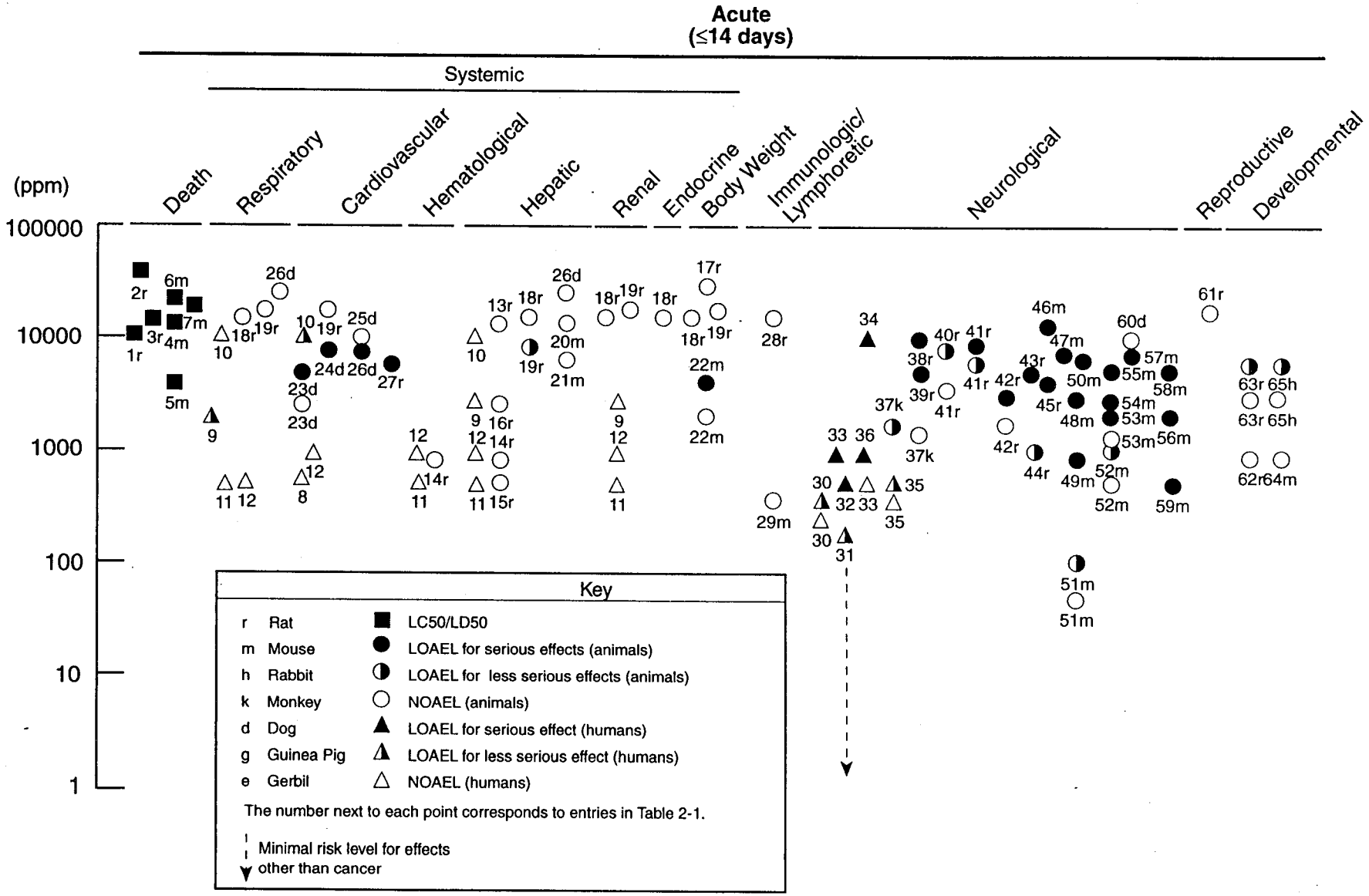


Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (continued)

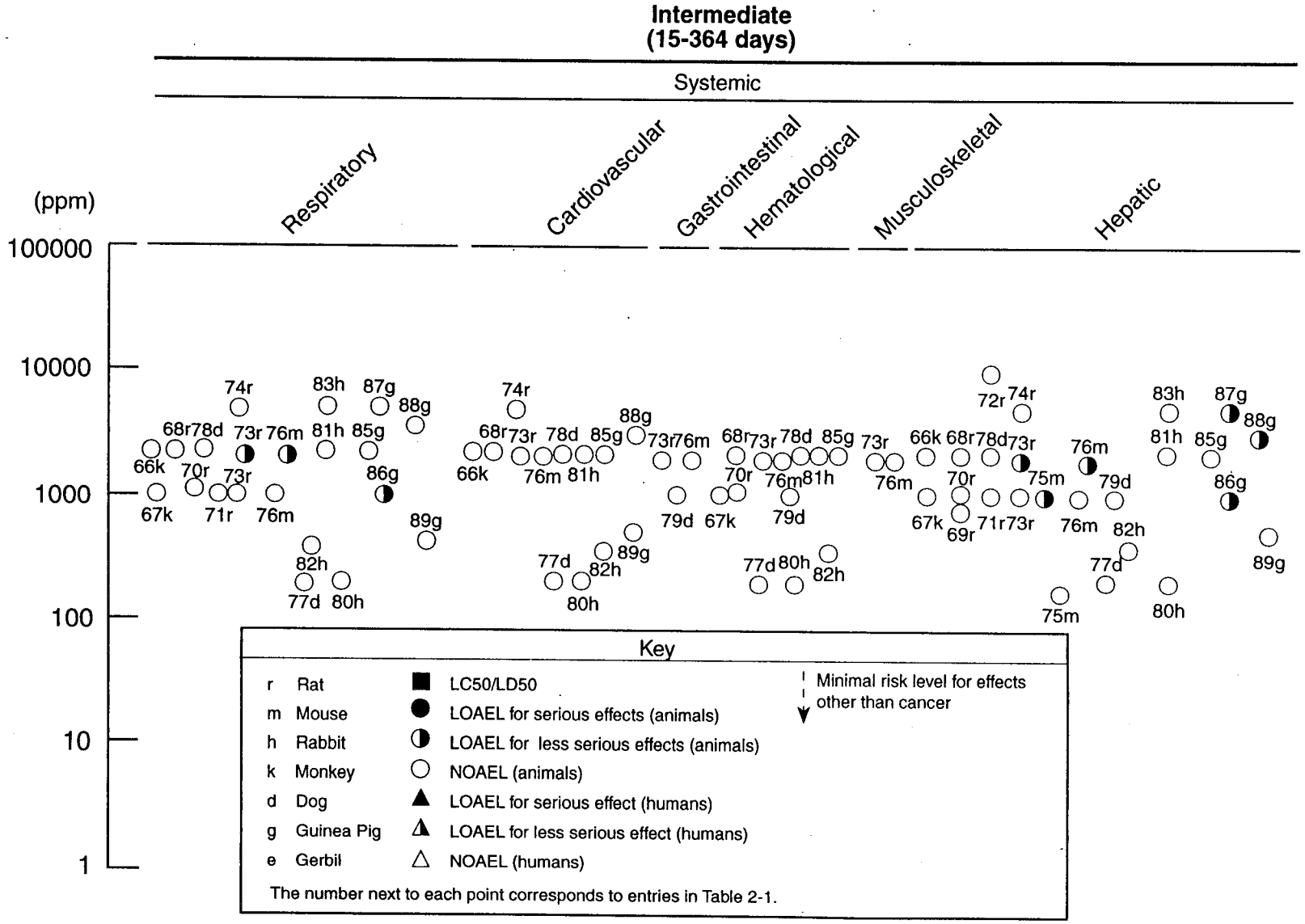


Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (continued)

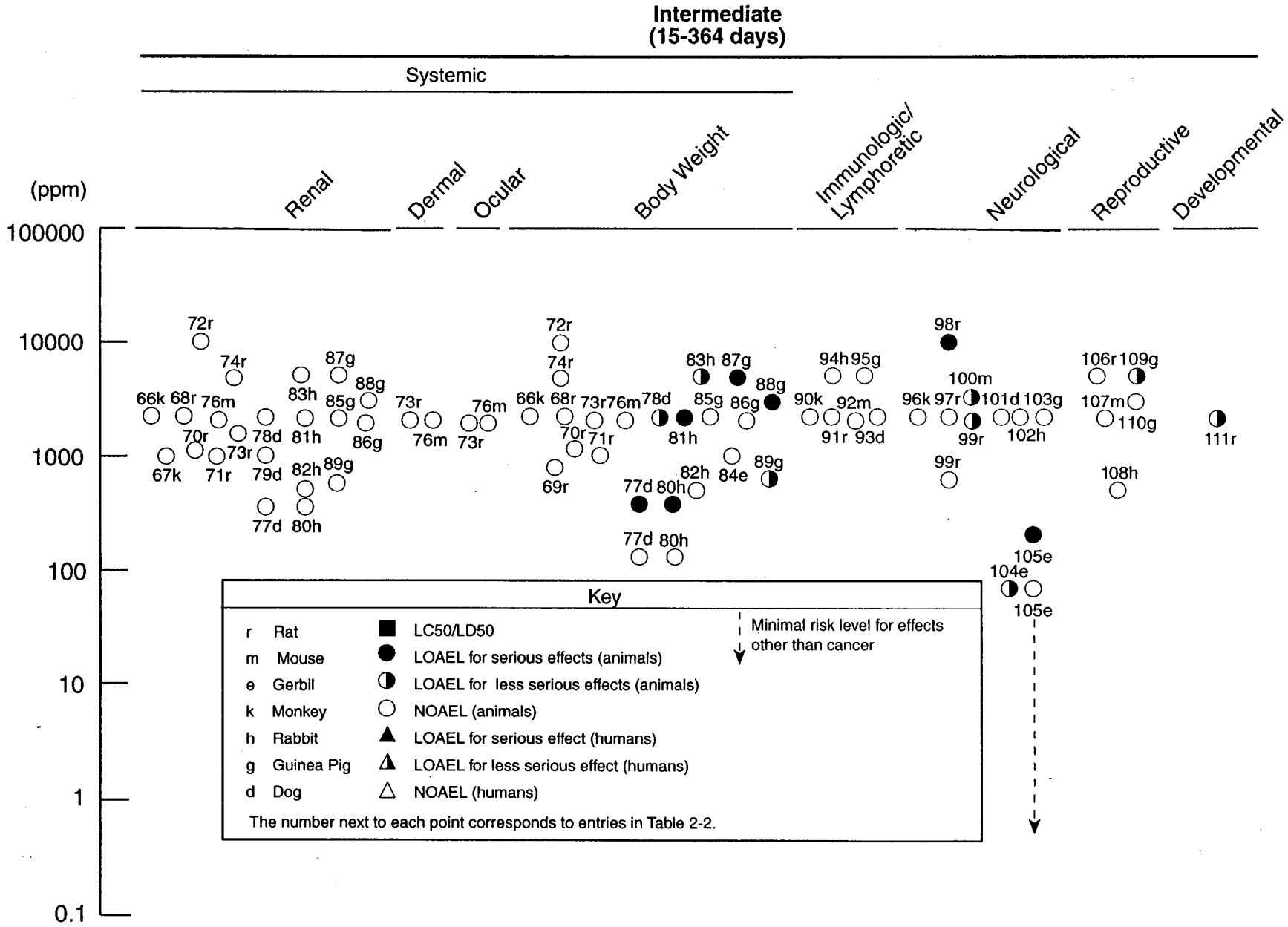
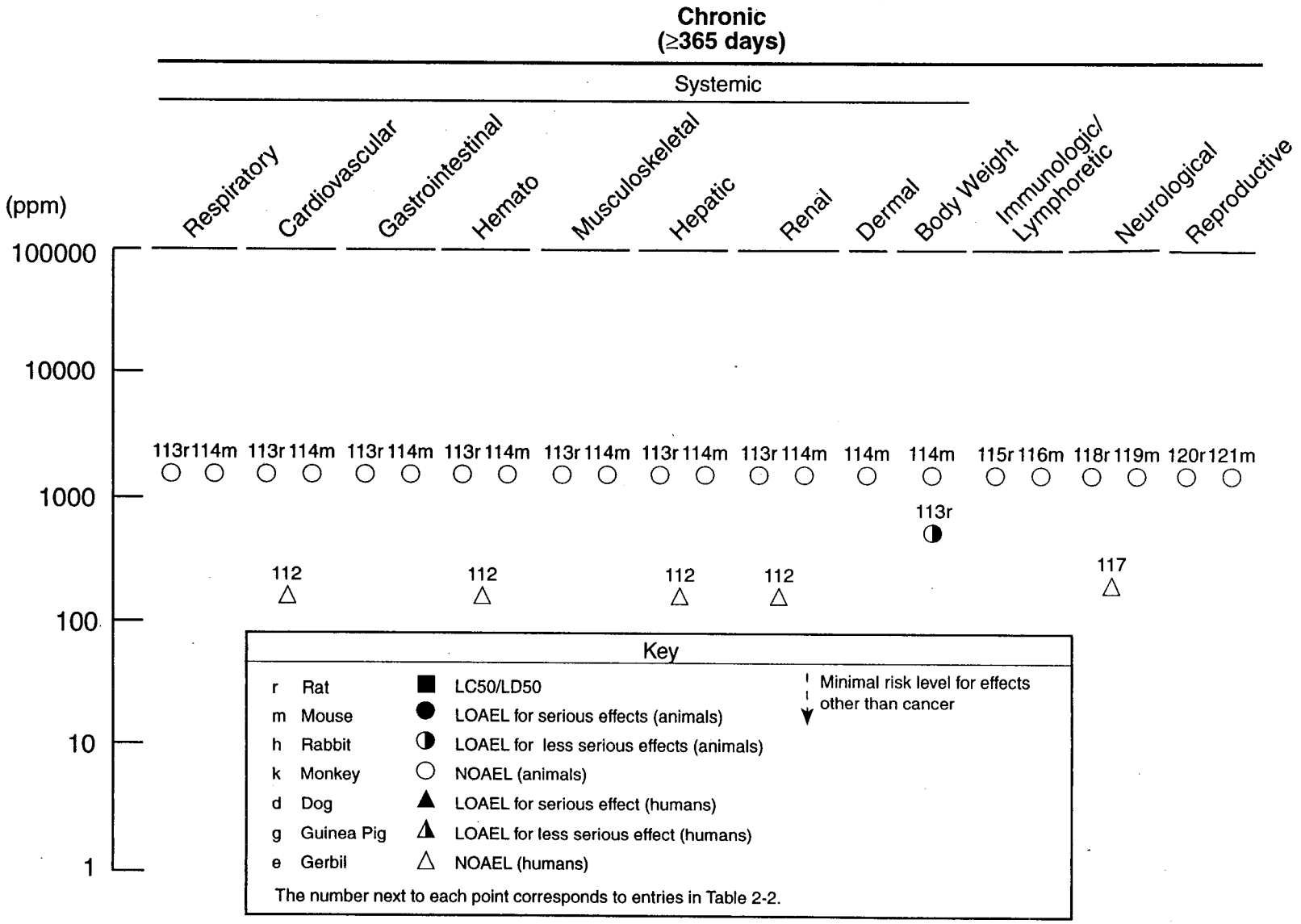


Figure 2-1. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation (continued)



and studies in animals indicate that long-term exposure to low or moderate 1,1,1-trichloroethane concentrations may not influence survival.

2.2.1.2 Systemic Effects

Respiratory Effects. In humans, acute exposure to high concentrations of 1,1,1-trichloroethane can produce respiratory depression (Kelly and Ruffing 1993), leading to death (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969). Respiratory depression may be a result of generalized central nervous system depression (see the discussion of Neurological Effects in this section). 1,1,1-Trichloroethane was not found to have produced irritation of respiratory mucous membranes. Acute exposure to lower concentrations of 1,1,1-trichloroethane in controlled studies did not affect respiratory rate or volume in humans (Domette and Jones 1960; Stewart et al. 1975; Torkelson et al. 1958). Chest radiographs from several (unspecified number) of twenty-eight workers exposed to an undetermined concentration of 1,1,1-trichloroethane for about 10 years showed changes consistent with early pneumoconiosis (fibrosis), but this was consistent with known exposure to asbestos and silica (Kelafant et al. 1994).

Death due to respiratory failure has been reported in several species of animals acutely exposed to high 1,1,1-trichloroethane concentrations (Adams et al. 1950; Krantz et al. 1959). Other data on respiratory effects in animals are limited to results of histological examinations of the lungs and related tissues. Tissue lesions were not found in rats or dogs exposed to high concentrations of 1,1,1-trichloroethane for short periods (Adams et al. 1950; Bonnet et al. 1980; Comish and Adefuin 1966; Herd et al. 1974). Exposure to moderate to high concentrations for intermediate periods (16 months) failed to produce pulmonary lesions in most species (Adams et al. 1950; Eben and Kimmerle 1974; MacEwen and Vemot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977), but irritation and inflammation occurred in the lungs of guinea pigs exposed to 1,000 ppm for 3 months (Torkelson et al. 1958). These effects were not found in other studies in which guinea pigs were exposed to lower concentrations or exposed for shorter durations (Adams et al. 1950; Prendergast et al. 1967; Torkelson et al. 1958). Rats and mice exposed to 2,000 ppm 1,1,1-trichloroethane for 3 months developed mild degeneration of the nasal olfactory epithelium (Calhoun et al. 1981). Chronic inhalation of moderate 1,1,1-trichloroethane concentrations did not produce lesions in the respiratory tissues of rats or mice (Quast et al. 1988).

The highest NOAEL values and all reliable LOAEL values for respiratory effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. Although lung irritation, inflammation, and olfactory epithelium degeneration were found in some species of laboratory animals exposed for intermediate durations in some studies, the weight of evidence suggests that respiratory failure in humans and animals is secondary to central nervous system depression and occurs only after acute exposure to very high concentrations.

Cardiovascular Effects. Inhalation of very high 1,1,1-trichloroethane concentrations for a short period can produce severe cardiac arrhythmias and death in humans. Arrhythmias are thought to be produced indirectly by 1,1,1-trichloroethane by sensitization of the heart to epinephrine (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). Cardiac sensitization to epinephrine has also been demonstrated in animals exposed to 1,1,1-trichloroethane (Clark and Tinston 1973). In addition, reduced blood pressure, occasionally severe, has been reported in humans following brief exposure to high concentrations of 1,1,1-trichloroethane (Domette and Jones 1960; Krantz et al. 1959). Acute exposure to lower concentrations (<1,000 ppm) did not affect clinical cardiovascular parameters such as blood pressure, pulse, heart rate, or electrocardiogram in the humans tested (Gamberale and Hultengren 1973; Torkelson et al. 1958). Myocardial injury, monitored by electrocardiography and echocardiography, was reported in the case of a young male who inhaled typewriter correction fluid (Wodka and Jeong 1991). It should be noted, however, that 1,1,1-trichloroethane may have been only one of several chemicals in the correction fluid.

In humans, long-term exposure to high 1,1,1-trichloroethane vapor concentrations can have toxic effects on the heart that persist beyond the period of exposure. While experiments in animals have shown that arrhythmias produced by 1,1,1-trichloroethane and epinephrine quickly subside after the cessation of exposure (Carlson 1981; Clark and Tinston 1973), three human cases involved ventricular arrhythmias that persisted for 2 weeks or more after solvent exposure ended (McLeod et al. 1987;. Wright and Strobl 1984). In all 3 cases, the subjects had been exposed repeatedly to high (unspecified) 1,1,1-trichloroethane concentrations. Echocardiograms revealed mild left ventricular dilation in one patient and slightly dilated left atrium in another, as well as impaired left ventricle function in both (McLeod et al. 1987). Chronic exposure (<250 ppm) to 1,1,1-trichloroethane had no effect on blood pressure, heart rate, or electrocardiogram in workers surveyed in a matched-pair epidemiology study (Kramer et al. 1978). Similar results were recently reported for a group of 28

workers exposed to unspecified, but high concentrations of 1,1,1-trichloroethane for about 10 years (Kelafant et al. 1994).

Sensitization of the heart to epinephrine-induced arrhythmias has been reported in both rabbits and dogs acutely exposed to high 1,1,1-trichloroethane concentrations (5,000-7,500 ppm) (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). The effect is rapid, occurring after only a few minutes of exposure, and transitory, quickly disappearing after the end of exposure. In rabbits, there was evidence that susceptibility to arrhythmia increased with exposure duration, and that 1,1,1-trichloroethane itself, not its metabolites, produced the sensitizing effect (Carlson 1981). Among dogs, the effect was similar in normal animals and those with experimentally induced myocardial infarctions; prior damage to the heart did not lower the threshold for cardiac sensitization produced by 1 ,l, 1 -trichloroethane (Trochimowicz et al. 1974).

Blood pressure was reduced in dogs acutely exposed to high concentrations of 1,1,1-trichloroethane (>7,500 ppm) (Herd et al. 1974; Krantz et al. 1959). This effect was studied in detail by Herd et al. (1974), who reported that the decrease in blood pressure began within 15 seconds of the start of exposure and grew more pronounced as exposure continued. At 8,000-15,000 ppm, the decrease in blood pressure was accompanied by increased myocardial contractility and cardiac output. A decrease in total peripheral resistance was apparently responsible for the decrease in blood pressure at these concentrations. At 20,000-25,000 ppm, blood pressure depression was caused by reductions in myocardial contractility and cardiac output. Blood pressure returned to pre-exposure values within 15 minutes after exposure, but indices of cardiac output and contractility required 45 minutes to recover. The dogs died if the blood pressure dropped too low. Histopathological changes in the heart were not found upon necropsy.

The arrhythmogenic and hypotensive properties of 1,1,1-trichloroethane have not been examined in animal studies of longer duration. Cardiovascular end points investigated in longer-term studies include heart weight and histopathology. No cardiovascular lesions were found among several animal species exposed to moderate to high concentrations (≤5,000 ppm) of 1,1,1-trichloroethane for ≤6 months (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Prendergast et al. 1967; Torkelson et al. 1958). Chronic inhalation of moderate concentrations (<2,000 ppm) of 1,1,1-trichloroethane did not produce cardiovascular lesions in rats or mice (Quast et al. 1988). The absence of effects detectable by routine histopathology in longer-term studies does not provide

convincing evidence for lack of cardiovascular effects, because even the marked acute effects were not accompanied by changes in histopathology. Overall, however, it appears that cardiotoxicity only occurs at very high exposure levels.

The highest NOAEL values and all reliable LOAEL values for cardiovascular effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l. Cardiovascular effects reported in humans include sensitization of the heart to epinephrine and decreased blood pressure. Both effects were found only after brief exposure to high 1,1,1-trichloroethane concentrations. These effects were also reported in animals, in which they were studied in greater detail. Some evidence from human case reports, although not conclusive, indicates that repeated exposure to high 1,1,1-trichloroethane concentrations may result in cardiovascular effects that persist for some time after the end of exposure. This possibility has not yet been assessed in laboratory animal investigation.

Gastrointestinal Effects. Nausea, vomiting, and diarrhea have been reported in humans exposed to high 1,1,1-trichloroethane concentrations by inhalation (Jones and Winter 1983; McCarthy and Jones 1983; Stewart 1971). Other gastrointestinal end points have not been examined in humans.

Gastrointestinal effects have not been reported in animals exposed to 1,1,1-trichloroethane, although vomiting is not possible in rodents and only histological end points have been studied in animals. Gastrointestinal lesions were not observed among several species of animals exposed to moderate to high concentrations of 1,1,1-trichloroethane for intermediate or chronic durations (Adams et al. 1950; Calhoun et al. 1981; MacEwen and Vemot 1974; Quast et al. 1988; Torkelson et al. 1958). The highest NOAEL values for gastrointestinal effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. Acute exposure to high 1,1,1-trichloroethane concentrations may produce nausea and related symptoms in humans, but evidence from animals suggests that longterm exposure will not produce histological changes.

Hematological Effects. No evidence exists that 1,1,1-trichloroethane produces hematological effects in humans. Hematological parameters, including white blood cell count, red blood cell count, hemoglobin, and hematocrit, were unchanged in humans acutely exposed to high or moderate concentrations of 1,1,1-trichloroethane (Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958; Wright and Strobl 1984). Hematological variables were similarly unaffected in workers chronically exposed to low-to-moderate levels of 1,1,1-trichloroethane in a matched-pair epidemiology study (Kramer et al.

1978). Hemolytic disease was suggested by increases in urinary urobilinogen in several people exposed to high levels of 1,1,1-trichloroethane (Stewart 1971; Stewart et al. 1961), but this possibility was discounted because there was no association between exposure and elevated urinary urobilinogen levels and because other indices of hematological effects were normal.

Hematological effects were not found in animals exposed to 1,1,1-trichloroethane. No exposure-related changes in hematological parameters were found following acute, intermediate, and chronic exposure to moderate to high 1,1,1-trichloroethane concentrations in several species of animals (Calhoun et al. 1981; Eben and Kimmerle 1974; Horiguchi and Horiguchi 1971; Koizumi et al. 1983; Krantz et al. 1959; MacEwen and Vemot 1974; Prendergast et al. 1967; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977).

The highest NOAEL values for hematological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-1. Existing data indicate that 1,1,1-trichloroethane does not produce hematological effects in humans or animals following inhalation exposure.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to 1,1,1-trichloroethane.

No musculoskeletal effects were found in animals exposed to 1,1,1-trichloroethane as assessed by histopathological examination. No lesions were found in the muscles or bones of a monkey exposed to a high 1,1,1-trichloroethane concentration for 74 days (Adams et al. 1950), or in rats and mice exposed for intermediate- or chronic-durations to moderate to high concentrations of the chemical (Calhoun et al. 1981; Quast et al. 1988).

The highest NOAEL values for musculoskeletal effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1. Based on existing data, 1,1,1-trichloroethane does not cause musculoskeletal effects in animals after chronic inhalation exposure. The relevance of this information to human health is unknown.

Hepatic Effects. Although there were no indications of liver effects in studies of controlled human exposure to 1,1,1-trichloroethane, data from case reports of overexposed humans suggest that this chemical may produce mild hepatic effects in humans exposed to high levels. ,

Serum levels of transaminases and other enzymes;used as indicators of hepatocellular damage (or damage to other tissues or organ systems), were not increased by acute exposure to moderate to high 1,1,1-trichloroethane concentrations in controlled human studies; liver function tests were likewise unaffected (Domette and Jones 1960; Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). However, some case studies of individuals exposed to high 1,1,1-trichloroethane concentrations did report elevated serum enzyme levels. Four individuals who had substantial occupational exposure to 1,1,1-trichloroethane had elevated serum glutamic oxaloacetic transaminase (SGOT) levels (Hodgson et al. 1989). An individual studied by Halevy et al. (1980) had elevated levels of serum bilirubin, lactate dehydrogenase (LDH), and alkaline phosphatase, as well as SGOT. It should be noted that SGOT and LDH are present in substantial amounts in myocardial cells as well as hepatocytes, and that elevations in these enzymes could have been the result of myocardial injury. Other exposed individuals did not have elevated serum enzyme levels (Stewart 1971; Wright and Strobl 1984). In some cases, histopathological examination revealed mild fatty changes in the liver of individuals exposed to high 1,1,1-trichloroethane concentrations (Caplan et al. 1976; Hall and Hine 1966; Hodgson et al. 1989). In another case, cholestasis was observed (Halevy et al. 1980). Nevertheless, hepatic changes were not observed in most cases.

Chronic exposure to low 1,1,1-trichloroethane levels (<250 ppm) did not affect serum chemistry parameters, including SGOT, serum glutamic pyruvic transaminase (SGPT), bilirubin, LDH, gamma-glutamyl transpeptidase, and alkaline phosphatase, in individuals tested as part of a matchedpair epidemiology study (Kramer et al. 1978). Results from tests for hepatic function were unremarkable in 28 workers exposed to unspecified, but high, concentrations of 1,1,1-trichloroethane for approximately 10 years (Kelafant et al. 1994).

1,1,1 -Trichloroethane produces mild hepatic effects in animals. The primary effects reported are mild histopathological changes in the liver and effects on liver enzyme activities. Acute exposure to high 1,1,1-trichloroethane concentrations did not affect serum transaminase levels in rats or mice (Carlson 1973; Comish and Adefuin 1966; Gehring 1968). An increase in transaminase levels would indicate damage to hepatocytes. The rate of deoxyribonucleic acid (DNA) synthesis in the liver also can be used as an indicator of hepatotoxicity. DNA synthesis would be expected to increase in response to cell death. Exposure to 1,100 ppm 1,1,1-trichloroethane produced a 67% increase in DNA synthesis in the. livers of exposed rats ,after 1 week; DNA synthesis returned to control levels throughout the rest of the 15-week study (Truffert et al. 1977). Corresponding histopathological changes were not found

throughout the study. Based on these data, measurement of DNA synthesis may be a more sensitive indicator of hepatocellular damage than increases in serum transaminase levels or the presence of readily observable lesions. However, these results have not been verified by additional testing. Only one study actually observed cell death following 1,1,1-trichloroethane exposure; occasional hepatocyte necrosis was seen in mice exposed to 1,000 ppm of 1,1,1-trichloroethane continuously for 14 weeks (McNutt et al. 1975). The first evidence of necrosis was not seen until after 10 weeks of exposure, but within 2 weeks of first occurrence, necrosis could be found in 40% of the exposed mice. In a study of chronic exposure, a slight decrease in the size of hepatocytes in the liver's portal region was seen in high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months (Quast et al. 1988).

The most widely reported hepatic effect in studies of 1,1,1-trichloroethane inhalation in animals is fat accumulation in the liver. Such changes are generally reversible and do not necessarily involve impairment of liver function. Histological examination following acute exposure to high concentrations revealed mild, reversible fatty changes in the livers of rats, but not dogs (Adams et al. 1950; Herd et al. 1974). Exposure duration was important in rats; effects were seen in those exposed for 7 hours, but not in those exposed to much higher concentrations for only 2 hours (Adams et al. 1950). In mice, 3-hour exposure to 800 ppm of 1,1,1-trichloroethane appeared to increase liver triglyceride levels, although controls were not included (Takahara 1986a). In studies of intermediate duration, exposure to moderate to high 1,1,1-trichloroethane concentrations produced fatty changes in the livers of rats, mice, and guinea pigs (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Fatty changes produced by 1,1,1-trichloroethane in the livers of mice continuously exposed to 1,000 ppm for 14 weeks were described in detail by McNutt et al. (1975). Prominent swelling of centrilobular hepatocytes was visible after the first week of exposure. Swelling was associated with the presence of numerous small vesicles in the cytoplasm. After 4 weeks, the number of microbodies in the cytoplasm was dramatically increased, and lysosomal vesicles were more prominent. Increased liver triglyceride levels were also reported in this study.

Studies of 1,1,1-trichloroethane's effects on liver enzyme activity are inconclusive. Acute inhalation of high concentrations induced the activity of liver microsomal enzymes (e.g., cytochrome P-450, NADPH cytochrome c reductase) in rats and mice (Fuller et al. 1970; Lal and Shah 1970). Continuous exposure to low 1,1,1-trichloroethane levels for 10 days also increased microsomal enzyme activity in rats (Koizumi et al. 1983); however, 5-day repeated exposure to a moderate concentration

decreased microsomal cytochrome P-450 enzyme activity in rats (Savolainen et al. 1977). Intermediate-duration exposure to a moderate concentration had no effect on microsomal enzyme levels in rats (Toftgaard et al. 1981).

The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1. Mild to moderate hepatic effects were occasionally reported in humans and animals exposed to 1,1,1-trichloroethane. These include indications of fatty liver and, in one case, cholestasis in humans and manifestations of hepatic necrosis and fatty changes in animals. These changes were not found in many studies, and results were mixed in many studies that did show effects. Evidence of hepatocellular damage and necrosis, changes in liver enzyme activity, and fat accumulation generally were reported following exposure to high concentrations in acute- and intermediate-duration studies in animals. The severity of the effects appears to be related to exposure dose and duration. It is unclear whether 1,1,1-trichloroethane may induce or inhibit microsomal enzyme activity in rats. In any case, the implications of effects on liver enzyme activity for toxicity are not clear, mainly because of the contradictory nature of the reported results.

Renal Effects. A few studies in humans have examined 1,1,1-trichloroethane's effects on select parameters of serum and urine chemistry that are related to renal function. Evidence of renal impairment was found in only one case report (Halevy et al. 1980). The individual in this case, who was exposed for 4 hours in a small room without ventilation (probably to high levels) presented with proteinuria, elevated blood creatinine, and reduced creatinine clearance, all of which were maximal at time of admission and returned to normal within 10 days. In addition to having prominent renal effects, this individual was unusual in having prominent liver effects and only minimal neurological effects. The authors suggested that an individual hypersensitivity might explain the atypical course of 1,1,1-trichloroethane intoxication. No effects were found on subsequent evaluations. No evidence of nephrotoxicity was found in other studies, although the end points examined, such as blood urea nitrogen (BUN), are only adequate for detecting serious decrements in function. An increase in the BUN level would indicate decreased elimination of nitrogenous waste by the kidneys (impairment of kidney function). Acute exposure to 1,1,1-trichloroethane had no effect on BUN or uric acid levels in humans exposed to high or moderate concentrations (Stewart 1971; Stewart et al. 1969, 1975; Wright and Strobl 1984). Chronic-duration exposure of workers to <250 ppm of 1,1,1-trichloroethane had no

effect on BUN, uric acid, or other serum indicators of nephrotoxicity in a matched-pair epidemiology study (Kramer et al. 1978).

Acute-duration exposure to high 1,1,1-trichloroethane concentrations failed to produce kidney lesions in rats (Adams et al. 1950; Bonnet et al. 1980; Comish and Adefuin 1966; Krantz et al. 1959), although relative kidney weight was increased slightly at 12,000 ppm in the one study in which it was measured (Adams et al. 1950). Exposure of several animal species to moderate to high concentrations for intermediate durations had no apparent effect on kidney weight or histopathology, or relevant serum chemistry parameters (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; MacEwen and Vemot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert .et al. 1977). Chronic inhalation of 1,1,1-trichloroethane did not affect the kidneys of rats or mice (Quast et al. 1988).

The kidney does not appear to be a target organ for 1,1,1-trichloroethane toxicity. The highest NOAEL values and all reliable LOAEL values for renal effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

Endocrine Effects. No studies were located regarding endocrine effects in humans following inhalation exposure to 1,1,1-trichloroethane.

Information in animals was limited to an acute-duration study in which no histopathological changes were seen in the adrenals of rats after a single 2-hour exposure to up to 15,000 ppm 1,1,1-trichloroetbane (Comish and Adefuin 1966). The NOAEL value for endocrine effects from this study is recorded in Table 2-l and plotted in Figure 2-l.

Derrmal Effects. No information was located regarding dermal effects in humans after inhalation exposure to 1,1,1-trichloroethane.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited dull fur coats (Evans and Balster 1993); this effect, however, was the result of direct contact with the chemical in the air (see Section 2.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the

incidence of dermal lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 2-1 and plotted in Figure 2-l.

Ocular Effects. Individuals briefly exposed to high 1,1,1-trichloroethane vapor concentrations reported mild eye irritation (Stewart et al. 1961). At moderate concentrations, no eye irritation was reported, even after 186 minutes.

Mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days exhibited eye irritation during exposure (Evans and Balster 1993). All of the above effects, however, were probably due to direct contact of the chemical in the air with the eye (see Section 2.2.3.2). Intermittent exposure of rats or mice to 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981) or to 1,500 ppm for 2 years (Quast et al. 1988) had no effect on the incidence of ocular lesions. NOAEL and LOAEL values derived from these studies are recorded in Table 2- 1 and plotted in Figure 2- 1.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to 1,1,1-trichloroethane.

Acute inhalation exposure to high concentrations of 1,1,1-trichloroethane did not affect body weight in rats (Adams et al. 1950; Bonnet et al. 1980; Cornish and Adefuin 1966). However, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane for 4 days experienced a 26% reduction in body weight throughout the exposure period (Evans and Balster 1993). In studies of intermediate duration, significant reductions in body weight gain were reported in guinea pigs exposed to 650 ppm (Adams et al. 1950) and rabbits and dogs exposed continuously to 377 ppm (Prendergast et al. 1967). Other intermediate-duration studies on a variety of species (including those mentioned above) found no compound-related effects on body growth, even at high concentrations (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; Kyrklund et al. 1988; MacEwen and Vernot 1974; Prendergast et al. 1967; Rosengren et al. 1985; Toftgaard et al. 1981; Torkelson et al. 1958; Truffert et al. 1977). Body weight gain was reduced in a concentration-dependent manner in female rats chronically exposed to 1,1,1-trichloroethane (Quast et al. 1988). Body growth was not affected in male rats or male or female mice chronically exposed to the same concentrations. Food consumption was not monitored in the available studies.

Changes in body weight can be produced in a number of ways (e.g., effects on palatability of food, absorption of nutrients, energy metabolism). In the case of 1,1,1-trichloroethane, it is possible that recurring central nervous system depression produced by repeated exposure may be responsible for the reduced body weight gain, by suppression of appetite and food intake. Due to the large number of factors that might affect body weight, assessing the potential relationship between isolated occurrences of reduced body weight gain in animals and possible effects of 1,1,1-trichloroethane on growth of humans is difficult. In any case no effects from levels found near NPL hazardous waste sites would be expected.

The highest NOAEL values and all reliable LOAEL values for body weight effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-l.

2.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects in humans after inhalation exposure to 1,1,1-trichloroethane. However, lymphoreticular effects, specifically spleen congestion, have been observed at autopsy in cases of acute accidental exposure to high concentrations of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969).

The effect of acute inhalation of 1,1,1-trichloroethane vapor on immune response in mice was studied by Aranyi et al. (1986). Mice received a single 3-hour exposure to 359 ppm of 1,1,1-trichloroethane. Susceptibility to respiratory infection was tested by challenge with *Streptococcus zooepidemicus* during exposure. Mortality was similar in test and control mice, indicating no effect on susceptibility to bacteria. To test the effect of inhalation exposure to 1,1,1-trichloroethane on the bactericidal activity of alveolar macrophages, mice were exposed to radiolabeled ^{35}S-*Klebsiella pneumoniae*, and the percentage of bacteria killed was recorded. No difference was found between test and control mice. The same results were found in both tests when mice were exposed under similar conditions for 5 days.

No histopathological alterations were observed in the spleen of rats exposed for 2 hours to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Longer-term studies of immunological effects in animals exposed to 1,1,1-trichloroethane by inhalation were limited to gross and microscopic examination of the spleen, thymus, and lymph nodes. No effect on spleen weight or, histopathology

was reported among several species exposed to moderate to high 1,1,1-trichloroethane concentrations in studies of intermediate duration (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958). No exposure-related effects were found upon histopathological examination of the spleen and thymus after chronic exposure to 11,750 ppm in rats and 1,500 ppm in mice (Quast et al. 1978, 1988).

The highest NOAEL values for immunological effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l. The existing data suggest that 1,1,1-trichloroethane may not produce toxic effects on the immune system, but sensitive immunological end points have not been examined in humans or animals.

2.2.1.4 Neurological Effects

1,1,1-Trichloroethane produces central nervous system depression, increasing with exposure concentration from mild motor impairment to euphoria, unconsciousness, and death in humans. Low concentrations reportedly produce impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual ,speed, and reaction time (Gamberale and Hultengren 1973; Mackay et al. 1987). Results using subjective assessment techniques indicate that behavioral changes may not be apparent to those exposed. Syntactic reasoning remained intact, and distractibility actually improved in the study by Mackay et al. (1987), suggesting that impairment produced by 1,1,1-trichloroethane may be task-specific. In other studies, comparable exposure conditions did not produce significant psychomotor effects (Salvini et al. 1971) or produced only weak effects (Savolainen et al. 1981). Although these studies examined some of the same parameters, such as reaction time, different analytical methods were used and different subpopulations tested. Based on the LOAEL of 175 ppm for reduced performance in psychomotor tests identified by Mackay et al. (1987), an acute inhalation MRL of 2 ppm was calculated as described in the footnote in Table 2-l.

Gross neurobehavioral effects, such as disturbances of equilibrium and coordination, occur in humans following acute exposure to 1,1,1-trichloroethane concentrations between 1,000 and 2,000 ppm (Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). These effects are more obvious at higher exposure concentrations (Torkelson et al. 1958). An increase was noted in the amplitude of alpha activity in electroencephalograms from individuals acutely exposed to moderate concentrations of 1,1,1-trichloroethane (Stewart et al. 1975). The significance of this effect is unknown, especially since

it persisted for several days, but it occurred at an exposure level that produced no effect on equilibrium or coordination. Visual evoked response was not affected in this study. Complaints of lightheadedness were also reported at moderate levels (Stewart et al. 1961). High 1,1,1-trichloroethane concentrations are inhaled intentionally by some people to experience these and related effects of intoxication.

Inhalation of high 1,1,1-trichloroethane concentrations can produce anesthesia in humans (Domette and Jones 1960). Domette and Jones (1960) tested the use of 1,1,1-trichloroethane as a general anesthetic in 50 hospital patients. The effective concentration for induction of anesthesia varied from 10,000 to 26,000 ppm. Onset of anesthesia was extremely rapid, taking place within 2 minutes of the start of exposure. Maintenance of light anesthesia for ≤2 hours required 6,000-22,500 ppm. Recovery from anesthesia occurred within 5 minutes of the end of exposure. In this study, 1,1,1-trichloroethane was co-administered with nitrous oxide and oxygen, and the effect of 1,1,1-trichloroethane without nitrous oxide was not measured.

Central nervous system depression can cause respiratory failure, the most prevalent cause of death in humans exposed to high 1,1,1-trichloroethane vapor concentrations (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969). Death from inhalation of 1,1,1-trichloroethane is often preceded by unconsciousness (Gresham and Treip 1983; Travers 1974). Half of the cases of industrial overexposure to 1,1,1-trichloroethane in Great Britain between 1961 and 1980 resulted in unconsciousness; most that did not indicate unconsciousness reported other central nervous system symptoms (McCarthy and Jones 1983). In one industrial .accident (Silverstein 1983), two affected men, as well as several of their rescuers, fell unconscious.

Two studies of long-term occupational exposures found no exposure-related neurological effects. In the ,first study, the highest exposure ranged from 200 to 990 ppm (Maroni et al. 1977). No exposurerelated effects were found, based on the results of subjective questionnaires, neurological examinations, and psychological tests. The authors reported that definite conclusions as to 1,1,1-trichloroethane's neurotoxicity in humans could not be drawn due to the small study population (seven or eight subjects per group) and what the authors felt was a relatively short exposure duration (6.7-year average). In the second study, workers exposed to l-46 ppm of 1,1,1-trichloroethane were also exposed to low concentrations of toluene (1-4 ppm) and xylene (0-7 ppm) (Cherry et al. 1983). No differences were found between exposed and unexposed workers in tests of reaction time and cognition. Subjective

responses indicated greater deterioration of mood in exposed workers, but this may not have been related to exposure. The 1,1,1-trichloroethane concentrations to which workers were exposed in this study were lower than those producing effects in experimental studies. A recent study of 28 subjects occupationally exposed to high (near anesthetic levels) unspecified concentrations of 1,1,1-trichloroethane over a period of 10 years revealed deficits in memory and in several components of balance (Kelafant et al. 1994); it was the investigators's opinion that the overall evidence was suggestive of toxic exposure.

The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, such as impaired performance in behavioral tests, ataxia, and unconsciousness, and are similar to those seen in humans. Relatively subtle behavioral effects in several species of animals have been reported following acute exposure to 1,1,1-trichloroethane concentrations in the 700-5,000 ppm range (Albee et al. 1990a; Balster et al. 1982; DeCeaurriz et al. 1983; Geller et al. 1982; Horiguchi and Horiguchi 1971; Kjellstrand et al. 1985a, 1990; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Woolverton and Balster 1981). These behavioral changes were readily reversible and generally involved effects on neuromuscular tests or learned behaviors. Studies using operant conditioning reflect effects of 1,1,1-trichloroethane in animals that are comparable to psychological changes in humans. Behavioral changes are generally considered to indicate neurological effects.

Neurophysiological changes have also been reported during acute inhalation exposure to 1,1,1-trichloroethane (Albee et al. 1990b). Exposure of rats to 2,000 ppm produced readily apparent changes in flash-evoked potential (FEP) and electroencephalogram (EEG), and more subtle changes in the somatosensory-evoked potential (SEP) when the rats were tested during exposure. Exposure to 1,000 ppm produced similar, but less marked, changes in the same measures. Continuous exposure of mice to moderate (500 ppm) concentrations of 1,1,1-trichloroethane for 4 days resulted in a withdrawal syndrome characterized by handling-induced seizures and reduced threshold to pentylenetetrazol-induced seizures after exposure ceased (Evans and Balster 1993). This effect could be prevented by central nervous system depressants, but not by anticonvulsants.

Acute exposure to high 1,1,1-trichloroethane concentrations produced intoxication and incoordination in rats and mice (Adams et al. 1950; Clark and Tinston 1982; Hougaard et al. 1984; Lazarew 1929), and elevation of the threshold for pentetrazole-induced seizures in mice (DeCeaurriz et al. 1981).

Exposure to 23,000 ppm produced ataxia, followed by unconsciousness and death due to respiratory failure in mice (Woolverton and Balster 1981). A progression from ataxia to lethargy, loss of motor function, and prostration produced by 1,1,1-trichloroethane has been observed in a variety of species, including rats, mice, dogs, and monkeys (Adams et al. 1950; Bonnet et al. 1980; Calhoun et al. 1988; Gehring 1968; Krantz et al. 1959; Lazarew 1929; Torkelson et al. 1958).

A recent comprehensive 13-week neurotoxicity study in rats included grip strength measures, a battery of observational measures, an electrophysiological test battery, and a neuropathology examination (Mattsson et al. 1993). The only notable finding was a significant deficit in forelimb grip performance in both male and female rats exposed to high levels (2,000 ppm) that persisted at least 7 weeks beyond the end of the exposure period. Histopathological and electrophysiological studies found no evidence of neuropathy in the forelimb that might account for this result. The authors hypothesized that sedative properties of 1,1,1-trichloroethane may have been responsible by allowing the animals to become more relaxed and, consequently, more habituated to the test procedure. No effects were found at moderate levels (630 ppm). The lack of neurophysiological effects at concentrations that produced such effects in the acute-duration study by Albee et al. (1990b) reflects the fact that testing was performed during exposure in the acute-duration study and 65 hours after the end of exposure in the intermediate-duration study.

Histopathological changes in the brain and spinal cord are not characteristic of 1,1,1-trichloroethane exposure and have not been reported when these structures have been examined (Herd et al. 1974; Krantz et al. 1959; Mattsson et al. 1993; Prendergast et al. 1967; Quast et al. 1978, 1988); however, researchers who have subjected gerbils to continuous, intermediate-duration exposure to 1,1,1-trichloroethane have reported changes in the brain that indicate physical damage. Four months after exposure had been discontinued, there was a significant increase in the level of glial fibrillary acid (GFA) protein in the sensorimotor cerebral cortex following exposure to 210 ppm of 1,1,1-trichloroethane (Rosengren et al. 1985). Since this protein is the main protein subunit of astroglial filaments and is found mainly in fibrillary astrocytes, an increase in its occurrence indicates the formation of astroglial fibrils, which are formed in response to brain injury. Therefore, increased GFA protein is associated with astrogliosis and central nervous system damage. These changes produced by 1,1,1-trichloroethane in this study were irreversible, or at least persistent. An intermediate-duration inhalation MRL of 0.7 ppm was derived for 1,1,1-trichloroethane based on the results of this study, as described in the footnote in Table 2-l. A second study, in which gerbils were exposed to 70 ppm of 1,1,1-trichloro-

ethane by the same protocol, was conducted by Karlsson et al. (1987). DNA content was used to measure cell density in different parts of the brain following exposure. Significantly decreased DNA content was found in the posterior cerebellar hemisphere, the anterior cerebellar vermis, and the hippocampus. These results could be caused by decreased cell density, possibly because of cell loss either by cell death or inhibition of nonneuronal cell acquisition in these areas, but the significance of these changes is uncertain. These methods of ascertaining physical damage to the brain have not been applied to other species.

1,1,1-Trichloroethane also produced changes in brain metabolism in rats and mice. Folbergrova et al. (1984) found a number of changes in cerebral cortical metabolism in rats exposed to high levels. Decreased glucose consumption and blood flow have also been documented in rats (Hougaard et al. 1984). Altered levels of cyclic nucleotides in the brains of mice exposed to low-to-moderate 1,1,1-trichloroethane concentrations were described by Nilsson (1986a, 1986b). The importance of the effects on cyclic nucleotides may lie in their altered capacity to act as secondary messengers within the cells, although the toxicological significance of this effect is unknown. No effect on the levels of protein, glutathione, acid proteinase, or ribonucleic acid (RNA) in the brain was found in rats acutely exposed to low concentrations of 1,1,1-trichloroethane (Savolainen et al. 1977). Continuous exposure to 1,200 ppm, but not lower doses, of 1,1,1-trichloroethane for 30 days altered the fatty acid composition of ethanolamine phosphoglyceride isolated from the cerebral cortex in rats (Kyrklund and Haglid 1991; Kyrklund et al. 1988).

1,1,1-Trichloroethane may share discriminate-stimulus properties with both pentobarbital and ethanol (Rees et al. 1987a, 1987b). Rees et al. (1987a) trained mice to press one lever in response to pentobarbital injection and another in response to saline injection. In this way, mice could “tell” the investigator when they were injected with pentobarbital. Upon inhalation of 1,1,1-trichloroethane for 20 minutes, there was a concentration-dependent increase in the percentage of time mice pressed the pentobarbital lever, indicating that the mice were generalizing the effects of pentobarbital to those of 1,1,1-trichloroethane. The results were similar in the second study (Rees et al. 1987b), in which the mice were trained to discriminate between ethanol and saline, and then exposed to 1,1,1-trichloroethane. These studies suggest that mice did not discriminate between the neurological effects of moderate to high concentrations of 1,1,1-trichloroethane and those of pentobarbital and ethanol.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-1. The acute depressive effect of 1,1,1-trichloroethane in both humans and animals progresses from subtle behavioral effects .at low-to-moderate concentrations to unconsciousness at high concentrations. There is evidence to suggest that 1,1,1-trichloroethane does not produce permanent neurological effects in humans. A study in gerbils, however, has produced evidence of lasting physical damage to the nervous system (astrogliosis) following prolonged continuous exposure to low concentrations (210 ppm) of this chemical. More data are needed to determine whether these results/observations are relevant for determining human risk.

2.2.1.5 Reproductive Effects

Taskinen et al. (1989) conducted a case-control epidemiology study to investigate the relationship between adverse pregnancy outcomes (spontaneous abortions and congenital malformations) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception. No relationship was found between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes.

Studies in several animal species found no evidence that 1,1,1-trichloroethane has adverse reproductive effects. Histological examination of male and female reproductive tissues following acute-, intermediate-, and chronic-duration exposure to 1,1,1-trichloroethane revealed no exposure-related changes in rats, mice, or rabbits (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977); however, varying degrees of testicular degeneration were observed in male guinea pigs exposed to 5,000 ppm 1,1,1-trichloroethane for 45 days (Adams et al. 1950). One study of intermediate duration used blood chemistry analyses to study reproductive effects. Continuous exposure to moderate levels of 1,1,1-trichloroethane vapor had no effect on butyrylcholinesterase activity in mice, which suggests that exposure did not have any effect on testosterone activity (Kjellstrand et al. 1985b). Testosterone appears to play a major role in regulating butyrylcholinesterase activity, and, although activity of this enzyme may change in the absence of an effect on testosterone, it is unlikely that an effect on testosterone levels would not be reflected by a change in butyrylcholinesterase activity.

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l. Based on the existing data, the reproductive system does not appear to be a target of 1,1,1-trichloroethane toxicity following inhalation exposure; however, the reproductive toxicity of this chemical cannot be evaluated fully due to the limited human data available and the lack of inhalation studies of reproductive function in animals.

2.2.1.6 Developmental Effects

Several case-control epidemiology studies investigated the relationship between adverse pregnancy outcomes (spontaneous abortions and/or congenital malformations) and maternal exposure to solvents, including 1,1,1-trichloroethane (Lindbohm et al. 1990; Taskinen et al. 1989; Windham et al. 1991). No clear evidence of a relationship between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes was found in any of these studies.

The potential developmental toxicity of inhaled 1,1,1-trichloroethane has been examined in rats and mice. Schwetz et al. (1975) exposed pregnant females of both species to moderate concentrations of 1,1,1-trichloroethane on days 6-l 5 of gestation. The only significant finding was an increase in absolute liver weight of maternal rats but not of maternal mice. Indices of embryo/fetotoxicity were comparable to controls. York et al. (1982) exposed female rats to 2,100 ppm of 1,1,1-trichloroethane for 2 weeks prior to mating and/or throughout pregnancy. There were no signs of maternal toxicity in any test group. A significant decrease in fetal body weight was observed in groups exposed either before and during pregnancy or during pregnancy only. Fetal body weights were not affected in the group exposed to 1,1,1-trichloroethane before pregnancy only. A significant increase in the incidence of delayed ossification and soft-tissue anomalies was observed only in the group that was exposed during both the premating period and gestation. Pup survival and weight gain were not affected by treatment, and neither was pup performance on neurobehavioral tests. There was no evidence of gross lesions upon necropsy at 12 months. Exposure of pregnant rats to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6-15 decreased fetal weight and delayed ossification of the cervical centrum (BRRC 1987a). Signs of maternal toxicity at this concentration included hypoactivity during exposure, perioral wetness, decreased food consumption, and increased water consumption. Maternal toxicity may have contributed to the fetotoxicity observed. Maternal toxicity and fetotoxicity were not observed in rats exposed to 3,000 ppm. Pregnant rabbits exposed to 6,000 ppm of 1,1,1-trichloroethane during gestation days 6-18 had decreased weight gain during exposure (BRRC 1987b). A

significant increase in the incidence of extra ribs was noted in the fetuses; however, this is an anomaly often associated with maternal toxicity, regardless of the test agent. No other evidence of embryotoxicity or teratogenicity was observed in this study.

The highest NOAEL values and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1. These data suggest that 1,1,1-trichloroethane is not a potent developmental toxin. Minor developmental effects characteristic of developmental delay were reported only at high doses and were usually accompanied by maternal toxicity.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to 1,1,1-trichloroethane. Genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to 1,1,1-trichloroethane. A study of 1,1,1-trichloroethane vapor carcinogenicity in Fischer 344 rats and B6C3F_1 mice was conducted by Quast et al. (1988). Animals were chronically exposed to moderate to high concentrations (150-l ,500 ppm) of the chemical. In rats, no significant differences in survival were observed between groups. Body weights of treated and control rats were comparable except for a slight but significant decrease in high-dose females. Slight microscopic changes were seen in the livers of high-dose male and female rats at 6, 12, and 18 months, but these effects were not distinguishable from normal geriatric changes at 24 months. In mice, no significant differences in survival, growth, or incidence of nonneoplastic lesions were observed between groups. Pairwise comparisons between control and treated groups revealed no differences in the incidence of tumors in rats or mice. Two positive dose-related trends were statistically significant, but neither was considered treatment related. In male rats, a positive trend was evident for the incidence of benign bilateral interstitial cell tumors of the testes, a highly spontaneous tumor in the strain of rats tested. This trend disappeared when all interstitial cell tumors were combined and re-analyzed. A statistically significant trend was found for an increase in the combined incidence of benign adenomas and cystadenomas in

the lacrimal gland of female mice, but the incidences were statistically comparable to concurrent controls as well as within the historical control range. The authors point out there was no increase in the incidence of lymphoreticular proliferative processes in either species in this study. This study by Quast et al. (1988) adequately demonstrated no evidence of carcinogenicity by the inhalation route at the exposure levels used, which approach the maximum tolerated dose (MTD). An apparent increase in the occurrence of immunoblastic lymphosarcomas of the lung was reported in rats tested in an oral carcinogenicity study (Maltoni et al. 1986), described in Section 2.2.2.8.

2.2.2 Oral Exposure

2.2.2.1 Death

A single report of human oral exposure to 1,1,1-trichloroethane was found in the literature. A man survived after accidentally drinking a single ≈600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). Clinical signs of toxicity were limited to a burning sensation in the throat, nausea, and incapacitating vomiting and diarrhea.

Torkelson et al. (1958) reported acute oral LD_{50} values of 12,300 and 10,300 mg/kg for male and female rats, respectively. LD_{50} values for other species include 11,240 mg/kg for mice, 9,470 mg/kg for guinea pigs, and 5,660 mg/kg for rabbits (Torkelson et al. 1958). A more recent study reported LD_{50} values of 17,148 and 12,996 mg/kg for male and female mice, respectively (Kinkead and Wolfe 1992). In 6-week studies, lethality was produced by gavage doses of 5,620 mg/kg/day in rats and 10,000 mg/kg/day in mice (NCI 1977). Repeated gavage doses of 2,500 mg/kg/day killed 5 of 15 rats within 50 days (Bruckner 1983). In chronic studies, effects on survival occurred at much lower doses. Survival decreased in rats exposed to 750 mgfkg/day and mice exposed to 2,807 mg/kg/day by gavage (NCI 1977). Chronic oral exposure to 500 mg/kg/day of 1,1,1-trichloroethane by gavage did not affect rat survival (Maltoni et al. 1986).

Exposure to high oral doses of 1,1,1-trichloroethane can be lethal to animals and, presumably, to humans. The levels associated with decreased survival in animals appeared to decrease as exposure duration increases. Reliable LD_{50} and LOAEL values for death are recorded in Table 2-2 and plotted inFigure 2-2.

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
	ACUTE EXPOSURE						
	Death						
1	Rat (NS)	once (G)				12300 M (LD50)	Torkelson et al. 1958
2	Rat (NS)	once (G)				10300 F (LD50)	Torkelson et al. 1958
3	Rat (Sprague-Dawley)	once (GO)				17148 M (LD50) 12996 F (LD50)	Kinkead and Wolfe 1992
4	Mouse (NS)	once (G)				11240 (LD50)	Torkelson et al. 1958
5	Rabbit (NS)	once (G)				5660 F (LD50)	Torkelson et al. 1958
6	Gn pig (NS)	once (G)				9470 M (LD50)	Torkelson et al. 1958
	Systemic						
7	Human	once	Cardio	600M			Stewart and Andrews 1966
			Gastro		600M (vomiting, diarrhea)		
			Hemato	600M			
			Hepatic		600M (increased serum bilirubin)		
			Renal	600M			

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
8	Rat (Sprague-Dawley)	once (GO)	Hepatic	4000M			Bruckner 1983
			Renal	4000M			
			Bd Wt	4000M			
9	Rat (Sprague-Dawley)	2 wk 5 d/wk (GO)	Hepatic	10000M			Bruckner 1983
			Renal	10000M			
			Bd Wt	500M		5000 M (about 20% reduced body weight gain)	
10	Rat (NS)	7 d 1 x/d (GO)	Hepatic	1650			Platt and Cockrill 1969
			Bd Wt	1650			
11	Rat (Sprague-Dawley)	once (GO)	Hepatic		1330M (ED50 for increased SGOT)		Tyson et al. 1983
12	Rat (Wistar)	1 d (GO)	Hepatic	1370M			Vainio et al. 1976
	Neurological						
13	Human	once		600M			Stewart and Andrews 1966
14	Rat (Fischer 344)	4 d 1 x/d (GO)			705 F (altered EEG, FEP, and SEP)		Spencer et al. 1990

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
15	Rat (Sprague-Dawley)	2 wk 5d/wk (GO)		500M		5000 M (hyperexcitability, narcosis)	Bruckner 1983
	INTERMEDIATE EXPOSURE						
	Death						
16	Rat (Sprague-Dawley)	12 wk 5 d/wk (GO)				2500 M (5/15 died)	Bruckner 1983
17	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)				5620 F (2/10 died)	NCI 1977
18	Mouse (B6C3F1)	6 wk 5 d/wk (GO)				10000 (8/10 died)	NCI 1977
	Systemic						
19	Rat (Sprague-Dawley)	12 wk 5 d/wk (GO)	Hepatic	2500M	5000M (mild, transient increased GPT, OCT)		Bruckner 1983
			Renal	5000M			
			Bd Wt	500M		2500 M (about 20% reduction in body weight gain)	
20	Rat (Osborne-Mendel)	6 wk 5 d/wk (GO)	Bd Wt	3160	5620 F (unspecified decrease in body weight gain)		NCI 1977

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
21	Mouse (B6C3F1)	6 wk 5 d/wk (GO)	Bd Wt	5620			NCI 1977
	Neurological						
22	Rat (Sprague-Dawley)	12 wk 5 d/wk (GO)		500M		2500 M (hyperactivity, narcosis)	Bruckner 1983
	Reproductive						
23	Rat (Sprague-Dawley)	70 d ad libitum (W)		2.96 F			NTP 1988a; George et al. 1989
24	Mouse (Swiss ICR)	25 wk ad libitum (W)		1000			Lane et al. 1982
	Developmental						
25	Rat (Sprague-Dawley)	40 d ad libitum (W)		2.4 F			NTP 1988b
26	Rat (CD)	70 d ad libitum (W)		3.50 F			NTP 1988a; George et al. 1989
27	Rat (Fischer-344	Gd 6-21 Ld 1-10 (GO)		750			Dow Chemical 1993

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
28	Mouse (Swiss ICR)	25 wk ad libitum (W)		1000			Lane et al. 1982
	CHRONIC EXPOSURE						
	Death						
29	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)				750 (survival decreased by approximately 50%)	NCI 1977
30	Mouse (B6C3F1)	78 wk 5 d/wk (GO)				2807 F (14% decreased survival)	NCI 1977
	Systemic						
31	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)	Resp	1500			NCI 1977
			Cardio	1500			
			Gastro	1500			
			Hemato	1500			
			Musc/skel	1500			
			Hepatic	1500			
			Renal	1500			
			Derm	1500			
			Bd Wt		750 (significant raduction in body weight gain, but not quantified)		

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key[a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
32	Rat (Sprague-Dawley)	104 wk 4-5 d/wk (GO)	Bd Wt		500 F (body weight gain reduced 12% after 80 weeks)		Maltoni et al. 1986
33	Mouse (B6C3F1)	78 wk 5 d/wk (GO)	Resp	5615			NCI 1977
			Cardio	5615			
			Gastro	5615			
			Hemato	5615			
			Musc/skel	5615			
			Hepatic	5615			
			Renal	5615			
			Derm	5615			
			Bd Wt		2807 (significant decrease in body weight gain, but not quantified)		
	Immunological/Lymphoreticular						
34	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977
35	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977
	Neurological						
36	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977

TABLE 2-2 Levels of Significant Exposure to 1,1,1-Trichloroethane - Oral (continued)

Key [a] to figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
37	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977
	Reproductive						
38	Rat (Osborne-Mendel)	78 wk 5 d/wk (GO)		1500			NCI 1977
39	Mouse (B6C3F1)	78 wk 5 d/wk (GO)		5615			NCI 1977

[a]The number corresponds to entries in Figure 2-2.

Bd Wt = body weight; Cardio = cardiological; d = day(s); Derm = dermal; ED_{50} = effective dose, 50%; EEG = electroencephalogram; F = female; FEP = flash evoked potential; (G) = gavage-not specified; Gastro = gastrointestinal; Gn pig = guinea pig; (GO) = gavage (oil); GPT = glutamic-pyruvic transaminase; Hemato = hematological; hr = hour(s); LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; OCT = ornithine carbamyl transferase; NS = not specified; Resp = respiratory; SEP = somatosensory evoked potential; SGOT = serum glutamate oxaloacetate transaminase; (W) = drinking water; w = week(s); x = (times)

Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral

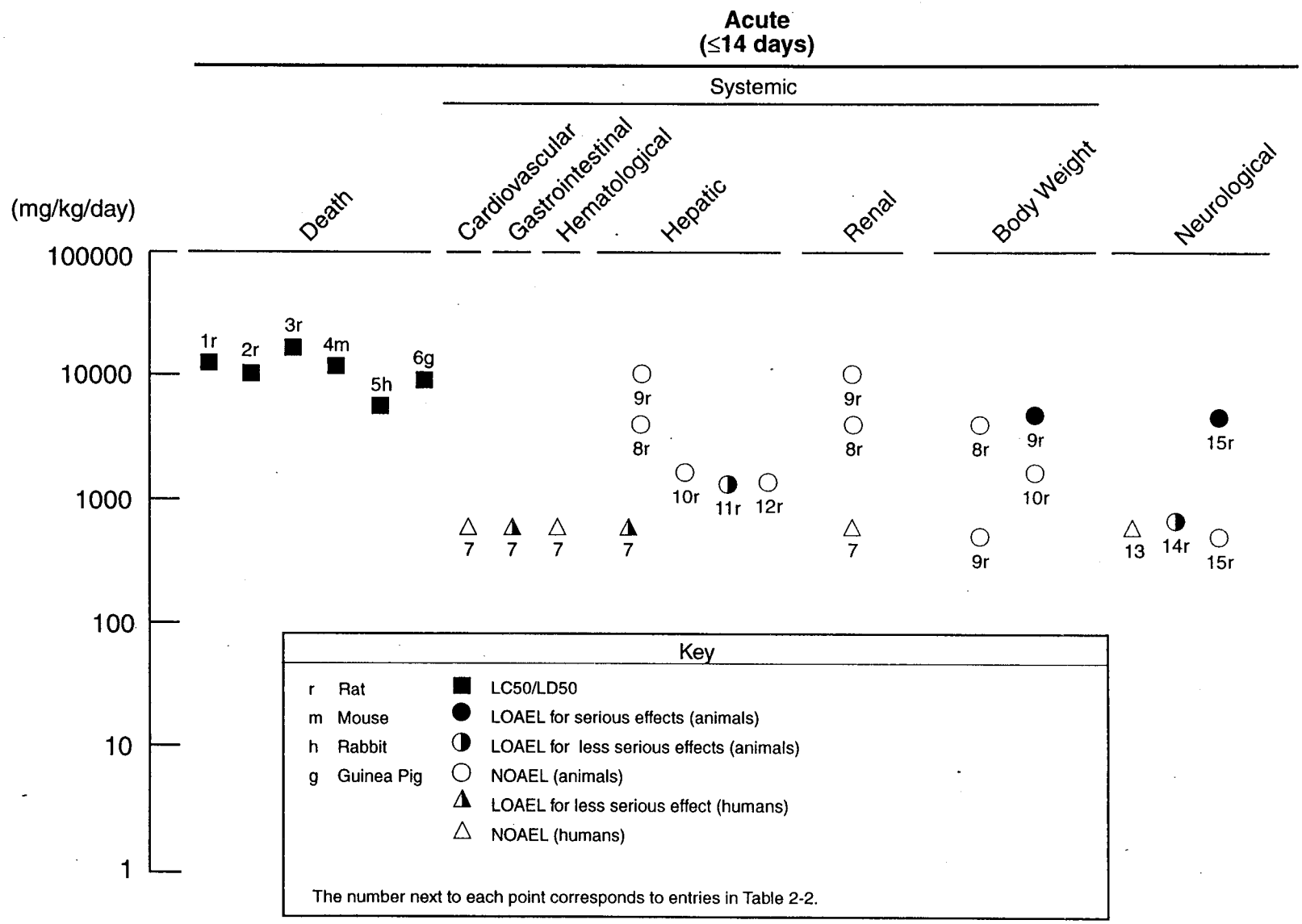


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (continued)

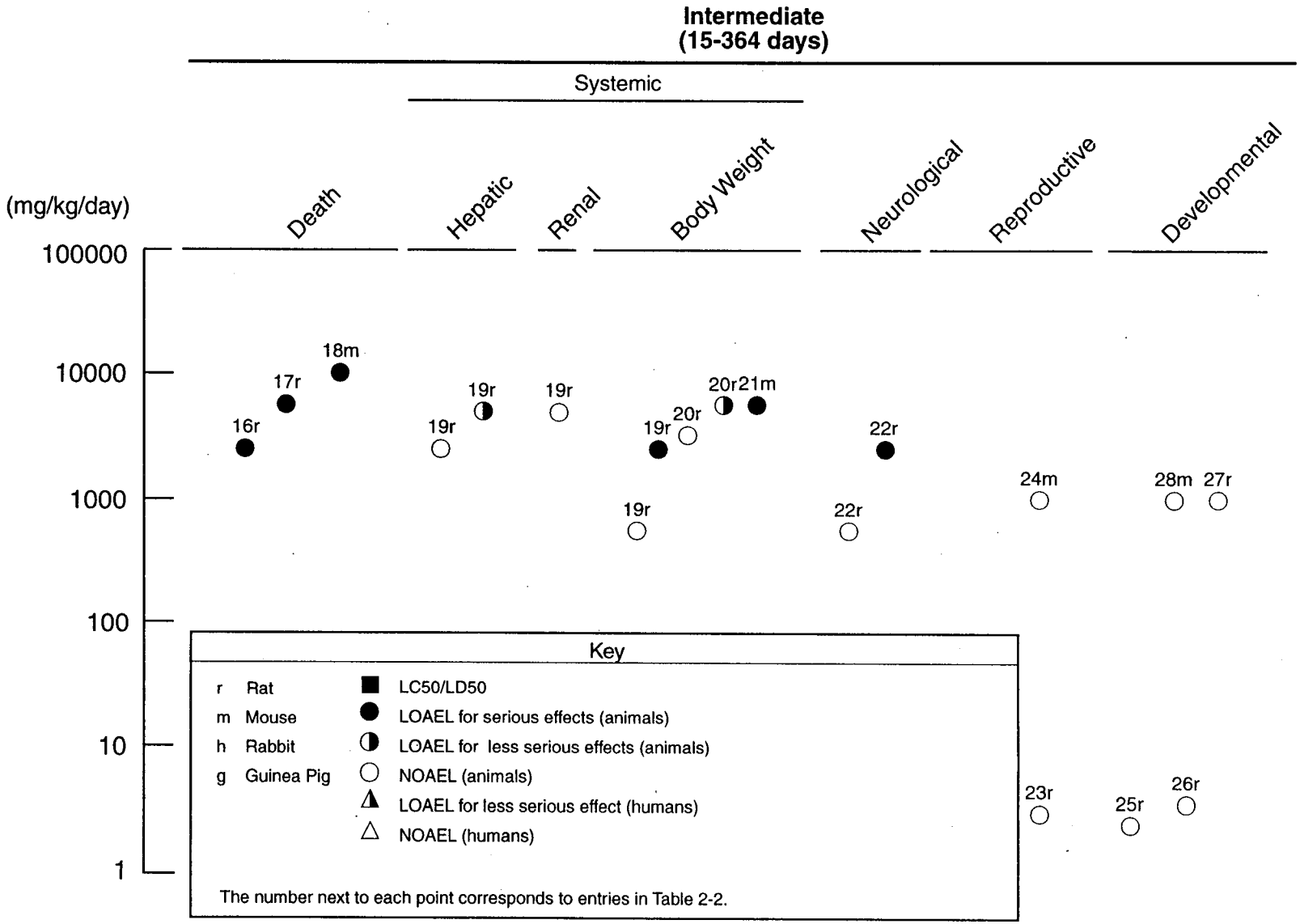
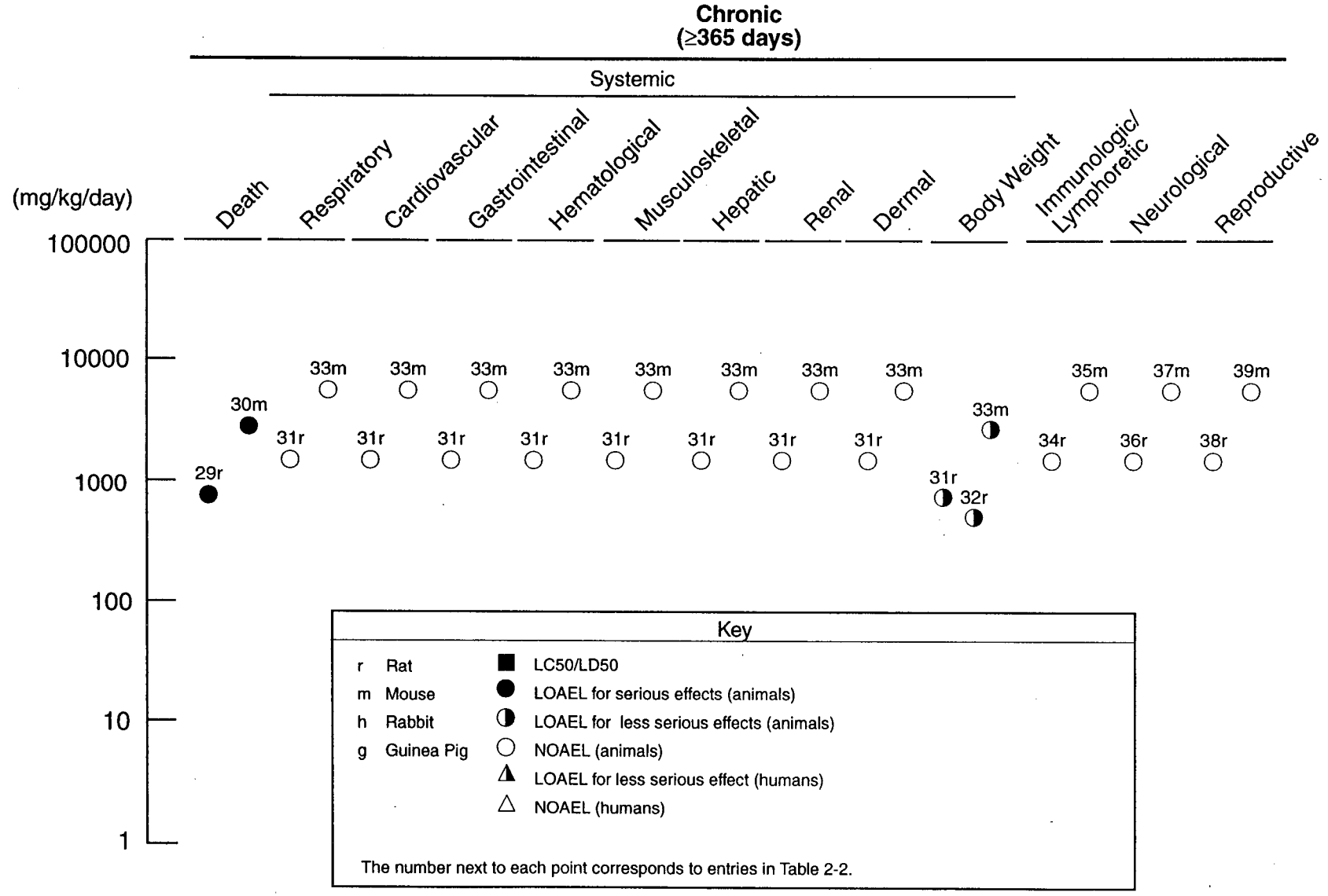


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (continued)



2.2.2.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,1,1-trichioroethane.

Only one oral study investigated the respiratory effects of 1,1,1-trichloroethane in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage did not affect the incidence of lesions in the lungs, trachea, or nasal passages (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2. Based on the negative results in the NCI (1977) study and the generally negative results in inhalation studies in which respiratory tissues came into direct contact with high levels (see Section 2.2.1.2), 1,1,1-trichloroethane is not expected to produce respiratory effects following ingestion in humans.

Cardiovascular Effects. Electrocardiogram readings were normal 4 hours after a man accidentally drank a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). Cardiovascular effects of ingested 1,1,1-trichloroethane have been investigated only by histopathological examination of exposed animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of lesions in the heart (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

The usefulness of histopathological heart examinations is limited, considering the findings of serious effects on cardiovascular function without pathological lesions in animals after acute exposure to high levels of 1,1,1-trichloroethane via inhalation. Therefore, existing data are insufficient to assess cardiovascular effects from oral exposure to 1,1,1-trichloroethane.

Gastrointestinal Effects. Severe vomiting and diarrhea began 1 hour after ingestion and continued for 6 hours in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966). The patient reported feeling a burning sensation in his mouth and throat immediately after swallowing the dose.

Gastrointestinal effects of orally administered 1,1,1-trichloroethane were investigated only by histopathological examination in animals. Chronic oral exposure of rats to 1,500 mg/kg/day and mice

to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the stomach, intestines, and pancreas (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

The results of the NCI (1977) study suggest that 1,1,1-trichloroethane does not produce gastrointestinal toxicity, while the case report of Stewart and Andrews (1966) shows that swallowing a large, undiluted dose of this chemical can produce severe gastrointestinal upset and some irritation of the throat.

Hematological Effects. Hematological parameters remained within normal limits in tests beginning 4 hours after exposure in a man who survived after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

Hematological effects were investigated only by histopathological examination in animals exposed to oral 1,1,1-trichloroethane. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the bone marrow (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

The limited data available suggest that ingested 1,1,1-trichloroethane does not produce hematological effects.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated musculoskeletal effects in animals exposed to 1,1,1-trichloroethane orally. Chronic oral exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day by gavage in oil did not affect the incidence of nonneoplastic lesions in the muscles or bones (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2.

Hepatic Effects. Stewart and Andrews (1966) reported a case in which a man survived drinking 1 ounce (600 mg/kg) of 1,1,1-trichloroethane. Serum transaminase levels remained within normal limits, but serum bilirubin levels became slightly elevated after 48 hours. Increased serum bilirubin

levels may result from reduced biliary excretion (i.e., cholestatic liver damage). Alternatively, hyperbilirubinemia may result from diminished hepatic conjugative metabolism of bilirubin.

Elevated SGOT levels, often seen in conjunction with hepatic damage and damage of other tissues, were reported in rats given a single oral dose of 1,330 mg/kg 1,1,1-trichloroethane (Tyson et al. 1983). Levels of SGPT, which is more specific for liver damage, remained unchanged in this study, however. Similar results in rats (little change in SGPT activity) were reported by others (Xia and Yu 1992). There were no indications of liver damage in rats given a single gavage dose of 4,000 mg/kg/day or repeated gavage doses of 10,000 mg/kg/day (Bruckner 1983). Data regarding the effect of 1,1,1-trichloroethane on the activity of rat liver enzymes are inconclusive. Increased liver microsomal and cytoplasmic protein content were found, although they were not accompanied by increases in activity of enzymes or increased liver weight (Platt and Cockrill 1969). Reduced levels of cytochrome P-450 and epoxide hydratase, suggesting inhibition of these enzymes, was reported in another study (Vainio et al. 1976). Bruckner (1983) found some evidence in rats of enzyme induction at low doses and inhibition at high doses. In an intermediate-duration study, mild liver effects (small increases in SGPT and ornithine carbamyl transferase [OCT]) occurred at 5,000 mg/kg/day (Bruckner 1983). Chronic gavage administration of 1,1,1-trichloroethane did not affect the incidence of nonneoplastic lesions in the livers of rats or mice (NCI 1977). The highest NOAEL values and all reliable LOAEL values for hepatic effects in each species and exposure duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Human and animal studies suggest that large amounts of ingested 1,1,1-trichloroethane may produce mild hepatotoxicity ; however, whether 1,1,1-trichloroethane is an inducer or inhibitor of biotransformation enzymes following oral exposure is unclear.

Renal Effects. BUN levels were not elevated 4 hours after a man accidentally ingested a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

No effects on kidney weight or histology were found in rats given a single gavage dose of 4,000 mg/kg/day, repeated doses of 10,000 mg/kg/day, or intermediate-duration exposure to 5,000 mg/kg/day (Bruckner 1983). There was a slight transient increase in BUN in the rats repeatedly given 10,000 mg/kg/day (Bruckner 1983). Chronic gavage exposure of rats to 1,500 mg/kg/day and

mice to 5,615 mg/kg/day did not affect the incidence of nonneoplastic lesions in the kidneys (NCI 1977). NOAEL values derived from these studies are recorded in Table 2-2 and plotted in Figure 2-2. Data from animals suggest that the kidney is not a target of 1,1,1-trichloroethane taken orally. Sensitive tests of renal function have not apparently been performed, however, in animals ingesting 1,1,1-trichloroethane.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to 1,1,1-trichloroethane.

Only one study investigated dermal effects following oral exposure in animals. Chronic oral exposure by gavage of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day of 1,1,1-trichloroethane did not affect the incidence of nonneoplastic skin lesions (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2. The scarcity of data regarding dermal effects in humans or animals after oral exposure to 1 ,l ,l -trichloroethane precludes assessing potential injury of this tissue.

Ocular Effects. No studies were located regarding ocular effects in humans or animals after oral exposure to 1,1,1-trichloroethane.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to 1,1,1-trichloroethane.

Several studies monitored body weight in animals dosed orally with 1,1,1-trichloroethane. Reduced body weight gain was produced in rats by repeated doses of 5,000 mg/kg/day in an acute study and 2,500 mg/kg/day in an intermediate-duration study (Bruckner 1983). In another study, reduced body weight gain was reported at 5,620 mg/kg/day in rats exposed for 6 weeks and 750 mg/kg/day in rats exposed for 78 weeks (NCI 1977). Body weight gain in rats was reduced by an even lower dose (500 mg/kg/day) in a second chronic study, but only after 80 weeks of exposure (Maltoni et al. 1986). In mice, 5,620 mg/kg/day did not affect body weight in a 6-week study, but 2,807 mg/kg/day was sufficient to reduce body weight gain in a 78-week study (NCI 1977). These limited data on the effects of orally administered 1,1,1-trichloroethane on body weight gain in animals suggest time- and dose-response relationships.

The highest NOAEL values and all reliable LOAEL values for body weight effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to 1,1,1-trichloroethane.

Immunological effects in animals were investigated only by histopathological examination of certain tissues. There was no effect on the incidence or type of nonneoplastic lesions in the thymus or spleen of rats or mice after chronic gavage exposure to high doses of 1,1,1-trichloroethane (NCI 1977). NOAEL values derived from this study are recorded in Table 2-2 and plotted in Figure 2-2. The scarcity of data pertaining to immunological effects in humans or animals after oral exposure to 1,1,1-trichloroethane precludes an assessment of immunotoxicity.

2.2.2.4 Neurological Effects

A thorough neurological examination (details not reported) found no abnormalities in a man who had ingested 600 mg/kg of 1,1,1-trichloroethane 4 hours earlier (Stewart and Andrews 1966).

Acute oral exposure of rats to 1,1,1-trichloroethane (705 mg/kg/day) did not result in behavior or appearance changes that could be detected after 2 days by a battery of observational measures, but did produce distinct neurophysiological alterations after 4 days. These alterations included marked changes in the flash-evoked potential (FEP) and electroencephalogram (EEG) recordings. Such effects are similar to those seen after inhalation exposure, and smaller changes in the somatosensory-evoked potential (SEP) (Spencer et al. 1990). Rats given high oral doses of 1,1,1-trichloroethane (≥2,500 mg/kg/day) exhibited a short period of hyperactivity, followed by a period of prolonged narcosis after daily dosing in acute- and intermediate-duration studies (Bruckner 1983). Neurological effects were investigated by histopathological examination of the brain and nerves in a chronic study (NCI 1977). There was no effect on the incidence or type of lesions in the brain or nerves of rats or mice after chronic gavage exposure to 1,1,1-trichloroethane (NCI 1977). Failure to detect neural lesions by routine histopathology in this study does not rule out the occurrence of neurological effects

following chronic oral exposure since physical changes in the brain did not accompany residual neurological effects seen in inhalation studies.

Reliable NOAEL and LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. Limited information is available regarding the neurological effects of 1,1,1-trichloroethane following oral exposure, but the observation of narcosis in the studies by Bruckner (1983) and the results of the acute neurophysiology study in rats suggest that the neurotoxicity of orally administered 1,1,1-trichloroethane may be similar to that observed following inhalation exposure.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to 1,1,1-trichloroethane. Reproductive effects were not found in animals orally exposed to 1,1,1-trichloroethane. A multigeneration reproduction study was conducted in mice by Lane et al. (1982). Male and female mice were exposed to 1,1,1-trichloroethane (≤1,000 mg/kg/day) in their drinking water. In the parental and F_1 generations, exposure began prior to mating and was continued through gestation and lactation. Exposure usually precedes mating by the length of the sperm cycle in studies of this type, but the duration of premating exposure for the parental generation was abbreviated in this study. Treatment did not affect maternal survival, body weight, or reproductive performance. In another study, rats were exposed to up to 3 mg 1,1,1-trichloroethane/kg/day in the drinking water from before mating through lactation (George et al. 1989; NTR 1988a). Neither maternal survival, body weight, fertility, nor the duration of gestation was affected. In a chronic-duration study in rats and mice, there was no effect on the incidence or type of nonneoplastic lesions in the prostate, seminal vesicles, testes, or epididymis in males, or the uterus or ovary in females (NCI 1977).

The highest NOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. There is no evidence that oral exposure to 1,1,1-trichloroethane produces reproductive effects in animals; however, low doses were administered in one study, and the duration of premating exposure was abbreviated in the other.

2.2.2.6 Developmental Effects

The possible relationship between developmental effects and exposure to 1,1,1-trichloroethane in the drinking water was investigated in a series of epidemiology studies (Deane et al. 1989; Wrensch et al. 1990a, 1990b). A leak in an underground storage tank resulted in contamination of well water with 1,1,1-trichloroethane and other chemicals. Levels of 1,1,1-trichloroethane were far higher than levels of other chemicals (1,700 ppb when first detected, reaching a maximum of 8,800 ppb after the well was closed). An excess of miscarriages and birth defects occurred in one exposed community but not in another. Hydrogeological modeling of water and contaminant distribution within the exposed communities showed that the leak was probably not responsible for the excessive adverse pregnancy outcomes in the one community, because estimated exposure to 1,1,1-trichloroethane was lower than in the other community. Average estimated exposure, in fact, was lower in areas reporting births with malformations than in those without. A related study, conducted on a larger scale, found an excess of major cardiac anomalies during the exposure period in the service area of the water company with the contaminated well, compared to the rest of the county (Santa Clara, California) (Swan et al. 1989). Detailed analysis of the temporal and spatial distribution of cases, however, did not support the hypothesis that contamination of the well produced these adverse effects.

Lane et al. (1982) investigated the developmental effects of 1,1,1-trichloraethane in mice in a multigeneration reproduction study modified to allow screening for teratogenic and dominant lethal effects. Mice of either sex were exposed to 1,1,1-trichloroethane in their drinking water. Exposure for the initial test mice and the subsequent F_1 generation began before mating and continued throughout gestation and lactation. Exposure is usually intended to precede mating by the length of the sperm cycle; however, in this study, the duration of premating exposure for the parental generation was abbreviated. No maternal toxicity was reported. There were no treatment-related embryotoxic or fetotoxic effects in either the F_1 or F_2 generation. Pup survival and body weight were also unaffected. There was no increase in the frequency of dominant lethal factors or in the incidence of skeletal or visceral, malformations in either generation.

The developmental effects of 1,1,1-trichloroethane were also studied in rats (George et al. 1989; NTF' 1988a, 1988b). Doses of up to 3 mg/kg/day of the chemical were administered in these studies to allow comparison with preliminary results of an earlier study (Dapson et al. 1984; Hutcheon et al. 1985) that reported increased incidences of cardiovascular anomalies at these doses. In the first study

(NTP 1988a), 1,1,1-trichloroethane was added to the drinking water of male and female rats before mating and through lactation. Exposure to 1,1,1 -trichloroethane had no effect on pup survival or body weight, or on the incidence of malformed pups. Particular attention was paid to developmental effects on the cardiovascular system. There was a high incidence of patent ductus arteriosus among pups that died on postnatal day 1 (10/28 exposed versus 0/8 control). Patent ductus arteriosus was found in only one treated pup (from the low-concentration group) sacrificed on postnatal day 4. No cardiovascular anomalies of any type were found in treated pups sacrificed on postnatal day 21, which was the time that Dapson et al. (1984) reported effects. The authors explain that patent ductus arteriosus is not unexpected in pups at the earlier time points (days 1 and 4), but do not address the apparent difference between treated and control groups on day 1. Most of the pups with patent ductus arteriosus were in the low-dose group; incidence was lower in the two higher-dose groups; and the effects were not statistically significant. These results suggest that 1,1,1-trichloroethane did not affect the development of patent ductus arteriosus in these rats.

In the second study (NTP 1988b), rats were exposed to up to 2.5 mg/kg/day in the drinking water from premating through gestation. Dams were sacrificed on day 20 of gestation, and the fetuses were given comprehensive teratological examinations. No embryotoxic or fetotoxic effects were reported. There was no effect on the incidence of external, visceral, or skeletal malformations. No cardiovascular abnormalities of any type were seen.

Recently, the results of a comprehensive study in rats (Dow Chemical 1993) became available. This study examined the neurobehavioral effects of 1,1,1-trichloroethane on the offspring of rats treated with the test material by gavage on gestation day 6 through lactation day 10. The doses used were 75, 250, and 750 mg 1,1,1-trichloroethane/kg/day. The end points examined included body weight, physical maturation landmarks, motor activity, functional observation battery, brain measurements and neuropathology, and evaluation of learning capacity, task performance and short-term memory. Although sporadic difference between treated animals and controls were found with some tests, these were either not statistically significant or not dose-related, suggesting that the highest dose tested, 750 mg/kg/day, was a NOAEL for the study.

The highest NOAEL values for developmental effects in each species are recorded in Table 2-2 and plotted in Figure 2-2. The weight of evidence in experimental animal studies suggests that 1,1,1-trichloroethane is not a developmental toxicant when administered orally; however, this

conclusion is limited by the use of low doses in some of the studies. Epidemiology studies found no evidence that exposure to 1,1,1-trichloroethane was responsible for the cluster of adverse pregnancy outcomes in Santa Clara County, California.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after oral exposure to 1,1,1-trichloroethane. Genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

Isacson et al. (1985) investigated the relationship between the presence of organic chemicals, including 1,1,1-trichloroethane, in drinking water and the incidence of cancer in Iowa residents. The authors contrasted towns that had detectable quantities of 1,1,1-trichloroethane in the water supply with those that did not and found no difference in the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in people over age 55. 1,1,1-Trichloroethane levels >0.1 μg/L (but unspecified) were detectable in this study. Assuming the average adult weighs 70 kg and drinks 2 liters of water per day, a concentration of 0.1 μg/L would produce a dose of approximately 0.000003 mg/kg/day. The authors concede that their data are not sensitive enough to support conclusions regarding the apparent lack of association between 1,1,1-trichloroethane in the water supply and cancer risk in humans. No other studies were located regarding risks of cancer in humans after oral exposure to 1,1,1-trichloroethane.

NCI (1977) conducted a bioassay for carcinogenicity of 1,1,1-trichloroethane in rats and mice. The test animals were exposed to high gavage doses of the chemical (750 or 1,500 mg/kg/day for rats and 2,807 or 5,615 mg/kg/day for mice) for 78 weeks. All animals were necropsied and the tissues examined histologically. The incidence and type of neoplasms observed were similar to those seen in untreated controls. Vehicle controls were not used in this study. There was a significant dose-related decrease in survival of both rats and mice. Among rats, no males and only 2-4% females survived to the end of the experiment. Among mice, 22-30% of treated males and 26-46% of treated females survived. Because the high rate of early mortality may have lowered the incidence of late-appearing tumors, the authors did not consider this study an adequate test of 1,1,1-trichloroethane carcinogenicity in either species.

A screening-type study using only one gavage dose level (500 mg/kg/day for 104 weeks) and a lessthan-optimal sample size (40 per sex) reported an apparent increase in leukemia incidence in rats (Maltoni et al. 1986). Survival appeared comparable between control and treatment groups, but no statistical analysis was performed. Body weight was reduced in females after 80 weeks of the experiment. Although tumor incidences were not analyzed statistically, an apparent increase in the total incidence of leukemias occurred, with 13 in treated rats and 4 in vehicle controls. The increase was due mainly to an increased incidence of immunoblastic lymphosarcomas in the lungs (seven in treated rats and one in controls). The biological and statistical significance of this finding cannot be determined because of the inherent limitations of the experimental design. The authors stated that, although definite conclusions could not be drawn based on this study, the results called for further experimentation to assess the carcinogenicity of 1,1,1-trichloroethane.

The inability to identify associations between human oral exposure and cancer incidence, as well as the limitations of the animal studies (i.e., high rate of early mortality, one dose level, small sample size), limit the assessment of potential carcinogenic effects in humans after oral exposure to 1,1,1-trichloroethane.

2.2.3 Dermal Exposure

Occupational exposure to 1,1,1-trichloroethane frequently involves both inhalation of and dermal contact with the chemical. There are many case reports of effects in individuals after occupational exposure to high levels of 1,1,1-trichloroethane, but inhalation appears to be the primary route of exposure in most such cases. Although dermal exposure may have contributed to the effects observed, these cases are discussed under Inhalation Exposure in Section 2.2.1. In a few cases, dermal exposure appeared to be more important, and these are discussed below. In all cases, except for superficial skin effects, any potential effect would likely be similar to inhalation effects at similar circulating blood levels.

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,1,1-trichloroethane.

Very high dose levels were required to cause death in animals after dermal exposure to 1,1,1-trichloroethane. Exposure to 15,800 mg/kg under a cuff killed <50% of the rabbits tested (Torkelson et al. 1958). Acute dermal exposure to lower doses did not cause death in rabbits or guinea pigs (Kinkead and Leahy 1987; Torkelson et al. 1958; Wahlberg and Boman 1979). Repeated-exposure studies employing doses up to 280 mg/kg/day (covered) or 500 mg/kg/day (uncovered) did not reveal any effect on mortality in rats or rabbits (Torkelson et al. 1958; Viola et al. 1981).

These limited data suggest that dermal exposure to 1,1,1-trichloroethane is lethal only at very high doses that could not be experienced under foreseeable circumstances. The LOAEL for death in acutely exposed rabbits is recorded in Table 2-3.

2.2.3.2 Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to 1,1,1-trichloroethane.

Respiratory effects in animals were investigated by pathological examination of the lungs in one study. Dermal exposure for 90 days to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no effect on lung weight or the incidence of gross or microscopic lung lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 2-3.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to 1,1,1-trichloroethane.

Cardiovascular effects in animals were investigated by histopathological examination in one study. Intermittent 90-day dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) had no. effect on heart weight or the incidence of heart lesions in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 2-3. Much higher doses may be required to produce effects by the dermal route; high vapor concentrations were required to produce cardiotoxic effects by inhalation exposure, and percutaneous absorption of 1,1,1-trichloroethane is much slower and less complete than pulmonary absorption.

TABLE 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Death						
Rabbit (NS)	1 d 24 hr/d				15800 (under 50% mortality)	Torkelson et al. 1958
Systemic						
Human	1 d 5 min/d	Derm		30 M (mild erythema)		Wahlberg 1984a
Human	10 d 1 x/d	Derm	2			Wahlberg 1984b
Rabbit (New Zealand)	1 d 24 hr/d	Bd Wt	2680 M			Kinkead and Leahy 1987
Rabbit (NS)	10 d 1x/d	Derm		35 (edema at application site)		Wahlberg 1984b
Rabbit (NS)	1 d	Ocular	50			Marzulli and Ruggles 1973
Gn pig (NS)	1 d	Bd Wt			7360 (30% reduction in body weight gain)	Wahlberg and Boman 1979
Gn pig (NS)	1 d 1/4 - 16 hr/d	Derm		1300 (epidermal degeneration)		Kronevi et al. 1981
Gn pig (NS)	10 d 1x/d	Derm		220 (edema at application site)		Wahlberg 1984b

TABLE 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
INTERMEDIATE EXPOSURE						
Systemic						
Rat (Wistar)	22 d 16 x	Gastro	280 M			Viola et al. 1981
		Hepatic		280 M (increased SGOT, OCT, GGT; hepatocellular damage)		
		Renal	280 M			
		Bd Wt			280 M (60% decrease in body weight gain)	
Rabbit (NS)	90 d 5 d/wk	Resp	500 M			Torkelson et al. 1958
		Cardio	500 M			
		Gastro	500 M			
		Hemato	500 M			
		Hepatic	500 M			
		Renal	500 M			
		Derm		15 M (mild skin irritation)		
		Bd Wt	500			
Immunological/Lymphoreticular						
Rabbit (NS)	90 d 5 d/wk		500 M			Torkelson et al. 1958
Neurological						
Rabbit (NS)	90 d 5 d/wk		500 F			Torkelson et al. 1958

TABLE 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
Reproductive						
Rabbit (NS)	90 d 5 d/wk		500 M			Torkelson et al. 1958

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Derm = dermal; Gastro = gastrointestinal; GGT = gamma-glutamyl transferase; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; min = minute(s); OCT = orthine carbamyl transferase; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; SGOT = serum glutamate oxaloacetate transaminase; wk = week(s); x = time(s)

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Gastrointestinal effects were not seen in animals dermally exposed to 1,1,1-trichloroethane. Rats exposed to 280 mg/kg/day of 1,1,1-trichloroethane under an occlusive dressing for 3 weeks showed no evidence of pancreatic damage, as determined by histopathological examination and serum lipase and amylase levels (Viola et al. 1981). Rabbits exposed to 500 mg/kg/day without occlusion for 90 days had no gross or microscopic lesions in the stomach or intestines (Torkelson et al. 1958).

These limited animal data suggest that dermal exposure to 1,1,1-trichloroethane will not result in gastrointestinal effects in humans. The NOAEL values for gastrointestinal effects in rats and rabbits are recorded in Table 2-3.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to 1,1,1-trichloroethane.

One study of hematological effects in dermally-exposed animals was located. Hematological parameters, including red blood cell count, white blood cell count, and hemoglobin, were unaffected by dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days in rabbits (Torkelson et al. 1958). A NOAEL derived from this study is recorded in Table 2-3. The scarcity of human and animal data limits the assessment of hematological effects that may be caused by dermal exposure to l,l, I-trichloroethane.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans or animals after dermal exposure to 1,1,1-trichloroethane.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to 1,1,1-trichloroethane.

Mild hepatic effects have been reported in animals after dermal exposure to 1,1,1-trichloroethane. Levels of SGOT, omithine carbamyl transferase, and gamma-glutamyl transferase, enzymes released into the serum from damaged hepatocytes, were significantly increased in rats dermally exposed to 280 mg/kg/day of 1,1,1-trichloroethane under occlusion in a 3-week study (Viola et al. 1981). Levels

of SGPT, another indicator of hepatic damage, were not affected. Histopathological effects, including damage to hepatocytes (fatty degeneration and mitochondrial swelling) and the presence of small focal intralobular inflammatory infiltrates, were seen in the exposed rats. A study in which rabbits were dermally exposed to higher doses of 1,1,1-trichloroethane for a longer period (but without occlusion) did not reveal histopathological effects in the liver or changes in liver weight (Torkelson et al. 1958).

Animal data suggest that dermal exposure to high doses of 1,1,1-trichloroethane may result in liver effects. Although too little information exists to allow a detailed evaluation, skin absorption is not likely to be a problem for foreseeable exposures. The NOAEL and LOAEL values for hepatic effects are recorded in Table 2-3.

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to 1,1,1-trichloroethane.

Renal effects were investigated in two animal studies. Histopathological examination of the kidneys found no lesions following repeated dermal exposure to 280 mg/kg/day (covered) in rats or 500 mg/kg/day (uncovered) in rabbits (Torkelson et al. 1958; Viola et al. 1981).

The scarcity of human and animal data limits the assessment of renal effects which may be caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL values for renal effects in rats and rabbits are recorded in Table 2-3.

Dermal Effects. Dermal exposure to 1,1,1-trichloroethane causes reversible effects in humans, which increase from mild irritation to chemical burns as exposure duration increases. Volunteers who immersed their thumbs in beakers of undiluted 1,1,1-trichloroethane for 30 minutes reported mild burning pain after ≈10 minutes of exposure (Stewart and Dodd 1964). Following exposure, mild erythema and fine scaling were visible on the thumb. The scaling was easily rinsed and the erythema disappeared within 1 hour. Similar results were obtained when the entire hand was immersed in the beaker, except that the burning sensation began earlier, became more intense, and then was replaced by a feeling of cold that continued 10 minutes after exposure ended. When the subject repeatedly alternated immersion in 1,1,1-trichloroethane with exposure to air, intense cold was produced by evaporation of 1,1,1-trichloroethane from the skin. The hand remained cold for 45 minutes after the end of exposure.

Brief dermal exposure to a small amount of 1,1,1-trichloroethane covered with a glass disk produced an immediate increase in blood flow that dropped back to pre-exposure levels after 1 hour (Wahlberg 1984a). Slight, transient erythema was visible from 10 to 20 minutes following exposure. The subject reported mild stinging and burning sensations. None of these effects were found when a smaller amount of 1,1,1-trichloroethane was allowed to spread freely on the subject's skin, probably due to rapid evaporation of the chemical (Wahlberg 1984a). Repeated uncovered application of a small amount had no effect on skin-fold thickness and produced no visible dermal reaction (Wahlberg 1984b).

One case of allergic contact dermatitis from 1,1,1-trichloroethane was located in the literature (Ingber 1991). A worker whose job included using 1,1,1-trichloroethane to clean metal plates developed severe acute hand eczema soon after starting the job. The eczema persisted throughout 3 years of employment. Patch tests at that time showed a positive reaction to 1,1,1-trichloroethane. The eczema disappeared after a few weeks when contact with 1,1,1-trichloroethane was avoided. The possibility the allergic reaction to being caused by 1,1,1-trichloroethane stabilizer was not discussed.

Assessments of the skin irritancy of 1,1,1-trichloroethane in animals reveal slight to moderate reactions. Based on single-application studies in rabbits, 1,1,1-trichloroethane was ranked as a moderate skin irritant by Duprat et al. (1976). Torkelson et al. (1958), however, reported only slight reddening and scaliness of rabbits' skin following a single application. Irritation observed following repeated application of the compound for 10 days was only slightly more noticeable and quickly disappeared after the end of treatment (Torkelson et al. 1958). Skin-fold thickness increased 41-81% in rabbits and guinea pigs exposed repeatedly to dermal applications of 1,1,1-trichloroethane, and visible erythema and edema were present within 24 to 72 hours of the original exposure (Wahlberg 1984b). Intermediate-duration exposure to doses ranging from 15 to 500 mg/kg/day produced only slight, reversible irritation at the application site (Torkelson et al. 1958). Lack of dose and exposure methodology information makes it difficult to compare the results of these studies, but the weight of evidence suggests that 1,1,1-trichloroethane is not a strong dermal irritant in animals.

Kronevi et al. (1981) studied cellular changes produced in the intact skin of guinea pigs by exposure to 1 mL of undiluted 1,1,1-trichloroethane under a cover glass for durations ranging from 15 minutes to 16 hours. No gross effects were observed, indicating that the overall irritation produced was minor, but a host of degenerative changes in the epidermis, including karyopyknosis, karyolysis, perinuclear

edema, and spongiosis, was found by histological examination. Focal junctional separation and cellular infiltration were observed in the upper part of the dermis. Effects were seen within 15 minutes of exposure, and some were still evident 16 hours later.

Exposure to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours caused the fur coat of mice to become dull (Evans and Balster 1993). This effect was most likely caused by direct contact of the chemical with the skin (see also Section 2.2.1.2).

Although extended dermal contact with relatively concentrated 1,1,1-trichloroethane may cause irritation and burning sensations of the skin of humans, most evidence in humans and animals indicates that this compound is not a strong skin irritant. There is one report of a 1,1,1-trichloroethane formulation acting as a skin sensitizer in humans. The highest NOAEL values and all reliable LOAEL values for dermal effects in each species and duration category are recorded in Table 2-3.

Ocular Effects. Individuals briefly exposed to high 1,1,1-trichloroethane vapor concentrations reported mild eye irritation (Stewart et al. 1961). This effect was most likely due to direct contact of the chemical with the eye.

Ocular administration of 1,1,1-trichloroethane caused only mild eye irritation in rabbits (Duprat et al. 1976; Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958). The study by Marzulli and Ruggles (1973) was a survey in which 10 laboratories conducted the Draize eye test in rabbits using 1,1,1-trichloroethane and reported little or no eye irritation.

Although eye irritation produced by direct application of 1,1,1-trichloroethane seems to be minor, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours exhibited eye irritation during exposure (Evans and Balster 1993). The highest NOAEL values and all reliable LOAEL values for ocular effects in each species and duration category are recorded in Table 2-3.

Body Weight Effects. No studies were located regarding body weight effects in humans after dermal exposure to 1,1,1-trichloroethane.

Animal studies have investigated the effect of topical 1,1,1-trichloroethane application on body weight. Acute exposure to 7,360 mg/kg of 1,1,1-trichloroethane (covered) decreased body weight gain in

guinea pigs (Wahlberg and Boman 1979). A lower dose had no effect on body weight in rabbits (Kinkead and Leahy 1987). Intermediate exposure to 280 mg/kg/day under occlusion reduced growth in rats (Viola et al. 1981). Exposure to a higher dose for a longer period did not affect rabbit body growth, but 1,1,1-trichloroethane was applied uncovered in this study (Torkelson et al. 1958). Food consumption was not monitored in these studies. Effects of 1,1,1-trichloroethane on body weight may have been produced by effects on appetite and food intake secondary to central nervous system depression, rather than physiological effects on growth and development.

The scarcity of human and animal data limits the assessment of body weight effects caused by dermal exposure to 1,1,1-trichloroethane. The NOAEL and LOAEL values for body weight changes are recorded in Table 2-3.

2.2.3.3 Immunological and Lymphoreticular Effects

One report of a worker who developed allergic contact dermatitis to a formulation of 1,1,1-trichloroethane (Ingber 1991) is discussed in more detail under Dermal Effects in Section 2.2.3.2.

In animals, immunological effects following dermal exposure were investigated only by histopathological examination. No lesions or weight changes were found in the spleens of rabbits exposed to moderate 1,1,1-trichloroethane levels (500 mg/kg/day; no occlusion) in a 90-day study (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 2-3. The scarcity of human and animal data precludes the assessment of potential effects on immune system tissues and function after dermal exposure to 1,1,1-trichloroethane.

2.2.3.4 Neurological Effects

Three women developed peripheral neuropathy after frequent, prolonged dermal contact with formulations of 1,1,1-trichloroethane and other chemicals at their workplace (Howse et al. 1989; Liss 1988). The women initially complained of numbness in their limbs, and subsequent nerve conduction studies showed alterations in peripheral nerve activity. The effect was diagnosed as primarily a distal sensory peripheral neuropathy. These cases were unusual because the effect was greater in the hands than in the feet, the reverse of most peripheral neuropathies. Sural nerve biopsies in two of the women performed 3-4 years after diagnosis revealed chronic neuropathy (axonopathy and

myelinopathy) (Liss 1988). The authors did not establish a causal relationship with 1,1,1-trichloroethane.

Dermal studies including tests of neurological function in animals were not located. Neurological effects were investigated by histopathological examination of the brain in one study. The value of these data is limited, however, since physical changes in the brain have not been found to accompany serious neurological effects in high level inhalation studies. No lesions or weight changes were found in the brains of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 2-3. These data are not sufficient for assessing the neurotoxicity of 1,1,1-trichloroethane after dermal exposure to the compound.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after dermal exposure to 1,1,1-trichloroethane.

Reproductive effects following dermal exposure were investigated only by histopathological examination in animals. No lesions or weight changes were found in the testes of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane (no occlusion) in a study of intermediate duration (Torkelson et al. 1958). The NOAEL value derived from this study is recorded in Table 2-3. The absence of human data, tests in female laboratory animals, and evaluation of reproductive function prevents an acceptable assessment of possible reproductive effects from dermally administered 1,1,1-trichloroethane.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to 1,1,1-trichloroethane.

2.2.3.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after dermal exposure to 1,1,1-trichloroethane. Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to 1,1,1 -trichloroethane.

2.3 TOXICOKINETICS

Upon first exposure, 1,1,1-trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals. As the duration of inhalation exposure increases, the percentage of absorption decreases because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. Animal studies have demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including to developing fetuses, with preferential distribution to fatty tissues. The predominant pathway of elimination of 1,1,1-trichloroethane in humans and animals, regardless of route of exposure, is exhalation of the unchanged compound. When exposure ceases, the compound is rapidly cleared from the body. In animal studies, only trace amounts of the compound remain in tissues within days of the termination of short-term exposure.

1,1,1-Trichloroethane is metabolized oxidatively, at low rates, to trichloroethanol and trichloroacetic acid by the cytochrome P-450 mixed-function oxidase system. These metabolites are excreted in the urine; other minor metabolites (carbon dioxide [CO_2] and acetylene) are excreted in expired air. (The acetylene is formed by reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply.) Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the route of exposure. The toxicokinetic behavior of 1,1,1-trichloroethane has the same qualitative pattern in humans, rats, and mice; however, some quantitative differences among these species have been observed, including a higher blood:air partition coefficient and an increased rate of metabolism in mice compared with rats and humans. Physiologically-based pharmacokinetic models have been developed to describe the

kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans; these models have been used to make interspecies and interroute extrapolations in estimating 1,1,1-trichloroethane exposure levels in humans that will produce (or not produce) toxic effects (Bogen and Hall 1989; Dallas et al. 1989; Leung 1992; Nolan et al. 1984; Reitz et al. 1988; USAF 1990).

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Data from experiments in which humans were exposed for short periods to 1,1,1-trichloroethane vapors indicate that the compound is rapidly and extensively absorbed by the respiratory system. 1,1,1-Trichloroethane was detected in the arterial blood of men within ≈10 seconds after exposure to 250 or 350 ppm (Astrand et al. 1973). When subjects held single breaths of air containing radiolabeled 1,1,1-trichioroethane for 15-40 seconds, alveolar concentrations decreased to between 10 and 20% of the initial concentrations, indicating extensive absorption upon initial exposure (Morgan et al. 1972a, 1972b). The extent of absorption of inhaled 1,1,1-trichloroethane decreases with continued exposure to the compound, as concentrations in alveolar air, blood, and tissues attain near equilibrium or steady state. Average lung retentions of 25-30% were measured in humans exposed to 35-350 ppm for 4-6 hours (i.e., the concentration of 1,1,1-trichloroethane in expired air after 4-6 hours of exposure equaled 70-75% of the inspired concentration) (Monster et al. 1979; Nolan et al. 1984). Physical exercise during 0.5-4-hour exposures increased systemic absorption of 1,1,1-trichloroethane, due to increased alveolar ventilation and cardiac output (Astrand et al. 1973; Monster et al. 1979). While steady-state levels in blood are approached within the first hours after exposure begins (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984), Nolan et al. (1984) predicted, using a physiologically-based kinetic model, that 12 consecutive and continuous daily exposures (presumably to concentrations of 350 ppm) would be required for l,I,l-trichloroethane in body tissues to reach 95% of steady state. Absorption is expected to be relatively low after steady state is reached, because the initial extensive absorption of 1,1,1-trichloroethane is the result of blood and tissue loading (which in turn are affected by respective blood:air and tissue:blood partition coefficients), tissue volumes and blood flows, and low metabolism. Bloodair partition coefficients for humans, rats, and mice were 2.53, 5.76, and 10.8, respectively (Reitz et al. 1988), meaning that small rodents will experience greater systemic uptake than humans, with mice receiving the highest dose. Mice also have the highest respiratory and circulatory rates, two additional factors that significantly

influence systemic absorption of I, 1,l -trichloroethane. 1,1,1-Trichloroethane is poorly metabolized (Dallas et al. 1989) (see Section 2.3.3.).

Animal experiments provide supporting evidence that inhaled 1,1,1-trichloroethane is rapidly and extensively absorbed and that the absorption, during short-term exposures, is influenced by ventilation rate. In rats exposed to 50 or 500 ppm, percentage uptake decreased from ≈80% at the onset of exposure to ≈50% after 2 hours of exposure to 50 or 500 ppm. 1,1,1-Trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure and approached steady-state concentrations within 2 hours (Dallas et al. 1989). In anesthetized dogs under regulated respiration conditions, 1,1,1-trichloroethane was detected in arterial blood within 2 minutes of the onset of exposure to 700, 1,500, or 3,000 ppm. Arterial blood concentrations approached steady-state levels within 1 hour at 700 ppm, but not at 1,500 or 3,000 ppm; absorption increased with increases in pulmonary ventilation rate (Hobara et al. 1982, 1983).

2.3.1.2 Oral Exposure

Data regarding the rate or extent of absorption of in,gested 1,1,1-trichloroethane in humans are not available, but based on extensive animal data, it is anticipated that oral absorption of 1,1,1-trichloroethane will be extensive in humans. Animal experiments indicate that 1,1,1-trichloroethane is rapidly and completely absorbed by the gastrointestinal tract. Maximum levels of 1,1,1-trichloroethane in venous blood of rats were detected within 10-15 minutes of gavage administration of a 14.2 mg/kg dose in water (Reitz et al. 1988). In experiments in which rats were given an 8-hour free access to drinking water containing [2-^{14}C]-labeled 1,1,1-trichloroethane, radioactivity in expired air, urine, and selected tissues (assayed 56 hours following cessation of access to the labeled water) represented 95.2% of the average dose of 116 mg/kg, indicating nearly complete absorption of the administered dose (Reitz et al. 1988). In experiments with rats and mice given single gavage doses of radiolabeled 1,1,1-trichloroethane in vegetable oil ranging from 100 to 3,000 mg/kg, dose-recovery in expired air ranged from 90 to 97% (RTI 1987). Nearly complete absorption of orally administered 1,1,1-trichloroethane was also indicated in experiments in which rats or mice were pretreated with daily doses of the compound in corn oil for 4 weeks (3,000 and 1,000 mg/kg/day for rats and mice, respectively) before radiolabeled compound was administered to measure absorption and elimination. Radioactivity in expired air and urine (collected for 48 hours after administration) accounted for 88-98% of the administered doses (Mitoma et al. 1985).

Absorption from the gastrointestinal tract is more rapid for 1,1,1-trichloroethane given in water than in vegetable oils, because the oils act as a reservoir for the chemical in the gut, so that most of the chemical remains in the oil in the gut until the oil is digested and absorbed.

2.3.1.3 Dermal Exposure

1,1,1-Trichloroethane is absorbed through human skin. The compound was detected in alveolar air of volunteers during 30minute skin absorption experiments (Stewart and Dodd 1964). The skin was exposed to the undiluted compound by thumb or hand immersion or topical application to the hand. The amount of 1,1,1-trichloroethane absorbed depended on the surface area of exposed skin and the method of exposure (i.e., immersion or topical application). 1,1,1-Trichloroethane concentrations in blood and alveolar air were 3-4 μg/mL and 2-5 ppm, respectively, immediately following the last of three daily, 2-hour exposures of 12.5 cm^2 areas of covered forearm skin in experiments with other subjects (Fukabori et al. 1977). Dermal absorption rates were 45.7 nmo/minute/cm^2 in mice after 2.92-cm^2 areas of skin were exposed to undiluted compound for 15 minutes under occluded conditions to prevent evaporative loss (Tsuruta 1975). In rats, ≈30% of a 2 mL volume of undiluted 1,1,1-trichloroethane was absorbed by a 3.1-cm^2 area of skin in 24 hours under occluded conditions (Morgan et al. 1991). It should be noted that under occluded conditions, which prevent evaporation, concentrated 1,1,1-trichloroethane will defat the skin and promote its own systemic absorption by disrupting the stratum comeum, the actual barrier to penetration. These are not conditions likely to occur in exposed people, however. There is no information available on the extent and rapidity of percutaneous absorption of 1,1,1-trichloroethane from aqueous solutions, a far more likely source of dermal contact, albeit at much lower dose rates.

1,1,1-Trichloroethane vapors will be absorbed through exposed skin to some extent, although absorption through the respiratory tract will predominate during whole-body exposure. Quantitative examination of the relative magnitudes of percutaneous and respiratory absorption in humans equipped with respiratory protection showed that a whole-body exposure to 600 ppm 1,1,1-trichloroethane for 3.5 hours would deliver a dermal dose equivalent to an absorbed inhalation dose from exposure to only ≈0.6 ppm over the same period (Riihimaki and Pfaffli 1978).

2.3.2 Distribution

2.3.2.1 inhalation Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane to human tissues after inhalation exposure. Nevertheless, 30 autopsies revealed detectable levels of the compound in subcutaneous and renal fat, liver, lung, and muscle (Alles et al. 1988).

Animal studies indicate that inhaled 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, with preferential distribution to fatty tissues. 1,1,1-Trichloroethane is rapidly cleared from tissues after exposure ceases (Holmberg et al. 1977; Schumann et al. 1982a; Takahara 1986b). Concentrations of 1,1,1-trichloroethane were higher in the liver than in the blood, kidneys, and brain of mice exposed to 10-10,000 ppm for 0.5-24 hours (fatty tissues were not analyzed separately in'this study) (Holmberg et al. 1977). In mice exposed to 1,000 ppm for 1 hour, tissue concentrations immediately after exposure displayed the following order: fat > liver > kidney > spleen = blood > lung = heart = brain (Takahara 1986b). In mice and rats exposed to 150 or 1,500 ppm 1,1,1-trichloroethane for 6 hours, concentrations were much (≈11-26-fold) higher in fatty tissue than concentrations in the liver and kidneys immediately following exposure (Schumann et al. 1982a). Experiments in which pregnant mice were exposed by inhalation to 1 ,l, 1-trichloroethane showed that the compound also is distributed to fetuses (Shimada 1988; Danielsson et al. 1986). Following a l-hour exposure of pregnant mice to 1,000 ppm, concentrations of 1,1,1-trichloroethane in maternal organs, fetuses, and placentas ranked in the following order: fat > blood > kidney > liver > placenta > brain > fetus (Shimada 1988).

2.3.2.2 Oral Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane to human tissue after oral exposure to the compound. Ingested 1,1,1-trichloroethane, however, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results of animal studies. Distribution of 1,1,1-trichloroethane to tissues will be governed by several factors, including tissue blood flow rate, tissue volume and tissue: blood partition coefficient, the latter factor being probably the most important. Following gavage administration of 1,1,1-trichloroethane in vegetable oil to rats

(100, 300, or 1,000 mg/kg) or mice (300, 1,000, or 3,000 mg/kg), the compound was distributed to tissues throughout the body, with preferential accumulation in fatty tissues (RTI 1987).

2.3.2.3 Dermal Exposure

No studies were located regarding the distribution of 1,1,1-trichloroethane among human or animal tissues following dermal exposure; however, dermally applied 1,1,1-trichloroethane, once absorbed, is probably widely distributed among tissues, with preferential accumulation in fatty tissues, based on results from oral and inhalation studies with animals.

2.3.2.4 Other Routes of Exposure

Measurements of the tissue distribution of ^{14}C-1,1,1-trichloroethane or its metabolites in rats or mice 24 hours after an intravenous injection indicate a distribution pattern similar to that after oral or inhalation exposure; adipose tissue contained higher concentrations than skeletal muscle, liver, or skin tissue (RTI 1987).

2.3.3 Metabolism

Metabolism appears to play a relatively minor role in the overall disposition of 1,1,1-trichloroethane in humans and animals. Only a small fraction of the absorbed dose (<10%) is metabolized; a large fraction of the absorbed dose is excreted unchanged in exhaled air, regardless of the exposure route. In humans exposed to 70 or 145 ppm 1,1,1-trichloroethane in air for 4 hours, an estimated 60-30% of the absorbed compound was excreted unchanged in exhaled breath (Monster et al. 1979). Metabolites in urine, trichloroethanol and trichloroacetic acid, collected for 70 hours postexposure represented approximately 2 and 0.5% of the 1,1,1-trichloroethane initially absorbed. In humans exposed to 35 or 350 ppm for 6 hours, >91% of absorbed 1,1,1-trichloroethane was excreted unchanged by the lungs, 5-6% was metabolized and excreted as trichloroethanol and trichloroacetic acid, and <1% remained in the body after 9 days (Nolan et al. 1984).

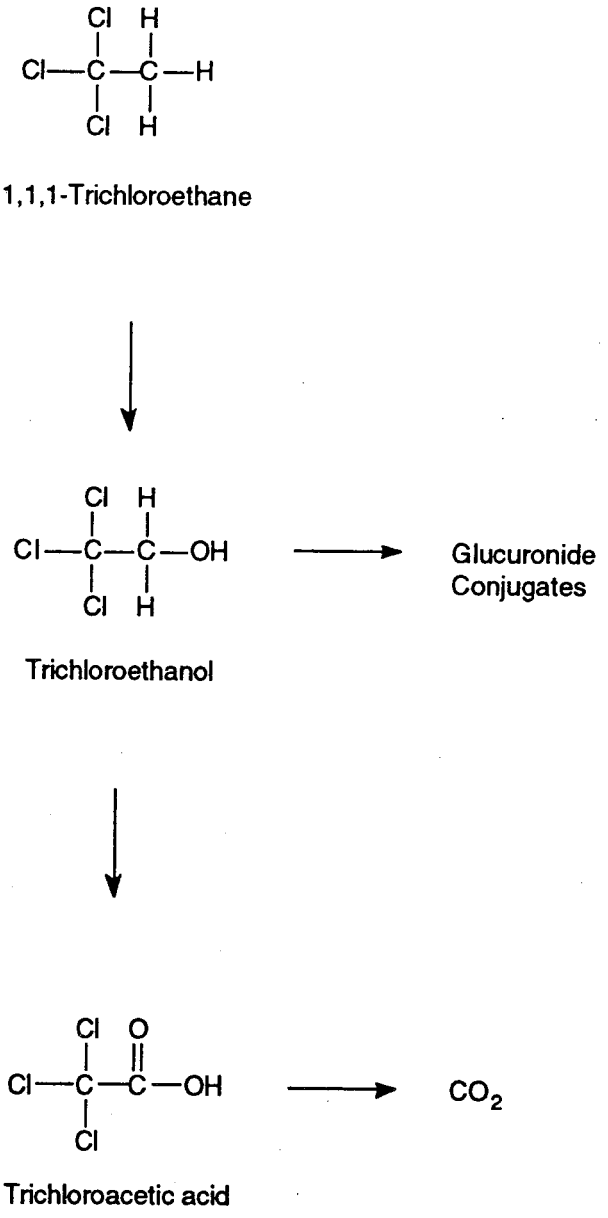
In rats and mice dosed by gavage with 1,1,1-trichloroethane in vegetable oil 5 days/week for 4 weeks, followed by a single dose of ^{14}C-labeled compound, 85.1 and 92.3% of the respective doses were recovered as unchanged compound in expired air; respective recovery percentages of metabolite

fractions (48 hours after administration) in rats and mice were 0.9 and 2.0% as CO_2 2.1 and 3.4% as metabolites in urine, and 1.2 and 0.7% as presumed metabolites remaining in the carcasses (Mitoma et al. 1985). Similarly, exhalation of unchanged compound was the predominant pathway for elimination of absorbed 1,1,1-trichloroethane, accounting for >90% of doses administered in drinking water studies with rats (Reitz et al. 1988) and in inhalation studies with rats and mice (Schumann et al. 1982a). Comparison of metabolic disposition in mice and rats indicated that mice metabolized 2-3 times more 1,1,1-trichloroethane on a body weight basis; however, in both species, metabolism was a dosedependent, saturable process that represented a minor route of elimination (Schumann et al. 1982a, 1982b).

Analysis of urine following human and animal exposure to 1,1,1-trichloroethane identified trichloroethanol, trichloroethanol glucuronide, and trichloroacetic acid as major metabolites of 1,1,1-trichloroethane; CO_2 identified in exhaled breath, is the other major metabolite (Kawai et al. 1991; Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; Schumann et al. 1982a). Figure 2-3 illustrates a general metabolic scheme for 1,1,1-trichloroethane. The initial oxidation step is thought to be catalyzed by the microsomal cytochrome P-450 mixed-function oxidase system. *In vitro* reaction mixtures containing rat hepatic microsomes and nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) oxidize 1,1,1-trichloroethane to trichloroethanol. 1,1,1-Trichloroethane metabolism significantly increased when microsomes from rats pretreated with phenobarbital, an inducer of certain isozymes of cytochrome P-450, were used. This finding provides supporting evidence of the involvement of this enzyme system in the metabolism, albeit limited, of 1,1,1-trichloroethane (Ivanetich and Van den Honert 1981;. Koizumi et al. 1983). The pathway for conversion of trichloroethanol to trichloroacetic acid presumably involves the intermediate. formation of chloral hydrate and may involve alcohol and aldehyde dehydrogenases or cytochrome P-450 mixed-function oxidases (Casciola and Ivanetich 1984; Ivanetich and Van den Honert 1981). Although trichloroacetic acid or chloral hydrate were not detected as *in vitro* metabolic products of. 1,1,1-trichloroethane with rat hepatic microsomal cytochrome P-450 preparations (Ivanetich and Van den Honert 1981; Koizumi et al. 1983), *in vitro* production of chloral hydrate from 1,1,1-trichloroethane was demonstrated in reaction mixtures containing rat nuclei cytochrome P-450 preparations (Casciola and Ivanetich 1984).

In vivo and *in vitro* evidence from rat experiments suggests that, under conditions of low oxygen supply, 1,1,1-trichloroethane can be reductively dechlorinated, to a limited extent, to dechlorinated

FIGURE 2-3. Metabolic Scheme for 1,1,1-Trichloroethane



radical intermediates and eventually to acetylene (Durk et al. 1992); in these experiments, exhaled acetylene accounted for <1% of metabolized 1,1,1-trichloroethane. The reductive dechlorination of 1,1,1-trichloroethane appears to be mediated by cytochrome P-450, since putative induction by phenobarbital treatment accelerated the *in vitro* and *in vivo* metabolic formation of acetylene. The reductive metabolic pathway is not indicated in Figure 2-3, because it apparently represents a very minor 1,1,1-trichloroethane metabolic pathway.

Repeated exposure of mice and rats to 1,1,1-trichloroethane apparently does not increase the relative importance of metabolism to the *in vivo* disposition of the compound (Schumann et al. 1982b), even though another research group reported that hepatic microsomes from rats exposed continuously for 10 days to 800 ppm of 1,1,1-trichloroethane displayed greater *in vitro* enzymatic activities for 1,1,1-trichloroethane oxidation than microsomes from fresh-air controls (Koizumi et al. 1983). Schumann et al. (1982b) found that repeated exposure of rats or mice to 1,500 ppm unlabeled 1,1,1-trichloroethane for 16 months did not alter the routes of excretion, the extent of metabolism, or the concentration of radioactivity in tissues after a 6-hour inhalation exposure to 1,500 ppm [2-^{14}C]-1,1,1-trichloroethane, compared with age-matched animals subjected to single 6-hour exposures. In general, studies regarding the effects of 1,1,1-trichloroethane on hepatic cytochrome P-450 enzyme levels are inconclusive. Although Koizumi et al. (1983) and others (Fuller et al. 1970; La1 and Shah 1970) reported that 1,1,1-trichloroethane induced hepatic cytochrome P-450 enzyme levels in rats, others observed no effects (Toftgaard et al. 1981) or inhibitory ,effects (Savolainen et al. 1977) in rats exposed to 1,1,1-trichloroethane.

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

After acute exposure, most inhaled 1,1,1-trichloroethane is rapidly excreted unchanged in expired air of humans and animals. Within 1 hour of administration, humans exhaled 44% of the radioactivity they had inhaled from a single breath of radiolabeled 1,1,1-trichloroethane (Morgan et al. 1970). Humans exposed to 70 or 145 ppm for 4 hours exhaled 60-80% of inhaled 1,1,1-trichloroethane unchanged during a 150-hour period after exposure (Monster et al. 1979). Other humans exposed to 35 or 350 ppm for 6 hours exhaled >91% of absorbed 1,1,1-trichloroethane as the unchanged compound within 9 days of exposure (Nolan et al. 1984). Similar observations were made in studies

of rats (Ikeda and Ohtsuji 1972; Schumann et al. 1982a, 1982b), mice (Schumann et al. 1982a, 1982b), and anesthetized dogs (Hobara et al. 1982). Nolan et al. (1984) described the temporal elimination pattern for 1,1,1-trichloroethane in blood and expired air of humans as "triexponential" and estimated half-lives of 44 minutes, 5.7 hours, and 53 hours for the initial, intermediate, and terminal phases, respectively. Raymer et al. (1991) used a two-compartment model to fit experimental observations of the temporal decrease in 1,1,1-trichloroethane concentrations in human breath samples collected for 4 hours after exposure to contaminated atmospheres; elimination half-lives ranged from 0.00 to 0.17 hours for the first compartment and from 1.80 to 6.08 hours for the second compartment.

Exhalation of CO_2 and urinary excretion of metabolites (trichloroethanol and trichloroacetic acid) represent minor elimination pathways for inhaled 1,1,1-trichloroethane. Nevertheless, observed correlations between urinary concentrations of 1,1,1-trichloroethane metabolites and exposure concentrations indicate that urine analysis may be a useful method of exposure assessment (Caperos et al. 1982; Ghittori et al. 1987; Imbriani et al. 1988; Kawai et al. 1991; Seki et al. 1975). Estimated half-lives for the elimination of trichloroethanol and trichloroacetic acid from human blood after inhalation exposures to 1,1,1-trichloroethane were 10-27 hours for trichloroethanol and 70-85 hours for trichloroacetic acid (Monster et al. 1979; Nolan et al. 1984). The long half-life of trichloroacetic acid is due to binding of this metabolite to plasma proteins. Daily occupational exposure to 1,1,1-trichloroethane progressively increased urinary metabolite levels during the workweek, while levels decreased over the weekend (Seki et al. 1975). This observation is consistent with observations of the rapid clearance of 1,1,1-trichloroethane and its metabolites from animal tissues after inhalation exposure (Dallas et al. 1989; Holmberg et al. 1977; Schumann et al. 1982a, 1982b; Takahara 1986a).

2.3.4.2 Oral Exposure

Humans eliminate ingested 1,1,1-trichloroethane in their exhaled breath (Stewart and Andrews 1966), but no studies were located that quantified excretion rates or the extent of excretion. The pattern of elimination is expected to be similar to that of inhaled 1,1,1-trichloroethane (i.e., exhalation of unchanged 1,1,1-trichloroethane should be the predominant route of excretion; exhalation of CO_2 and urinary excretion of other metabolites are minor routes). This pattern has been observed in animals after inhalation (see Section 2.3.4.1) and oral exposure (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987). In rats exposed to 1,1,1-trichloroethane in drinking water for 8 hours (total dose of 116 mg/kg), the primary route of excretion was rapid elimination of unchanged 1,1,1-trichloroethane in

expired air; only 3% of the ingested dose was metabolized (Reitz et al. 1988). Essentially all of the ingested 1,1,1-trichloroethane was excreted within 30 hours. Similar results were obtained in gavage studies with rats and mice (Mitoma et al. 1985; RTI 1987).

2.3.4.3 Dermal Exposure

The pattern of excretion in humans after dermal exposure is expected to be similar to that of inhaled 1,1,1-trichloroethane: rapid exhalation of 1,1,1-trichloroethane in expired air is the major excretion route; exhalation of CO_2 and urinary excretion of other metabolites are minor routes (see Section 2.3.4.1). Several studies have measured 1,1,1-trichloroethane in the expired breath of humans after (and during) short-term dermal exposure to 1,1,1-trichloroethane (Fukabori et al. 1977; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964), but 1,1,1-trichloroethane exhalation as a percentage of absorbed dose was not quantitated in these studies.

2.3.4.4 Other Routes of Exposure

Results in animals given 1,1,1-trichloroethane injections indicate that excretion patterns in animals are similar regardless of route. In mice given intraperitoneal injections of 1,1,1-trichloroethane, 88% of the dose was excreted unchanged in expired air, and 1% was excreted as metabolites in urine (Takahara 1986b). In rats given intraperitoneal injections, 98.7% of the dose was exhaled as unchanged 1,1,1-trichloroethane (Hake et al. 1960). Within 24 hours of intravenous injection of radiolabeled 1,1,1-trichloroethane, exhalation of radioactivity accounted for 91 and 80% of the administered doses in rats and mice, respectively; only trace amounts of radioactivity remained in the tissues after 24 hours (RTI 1987). In dogs, 60-70% of intravenously injected 1,1,1-trichloroethane was excreted in expired air within 1 hour (Hobara et al. 1981).

2.3.5 Mechanisms of Action

1,1,1-Trichloroethane is rapidly and extensively absorbed from the lungs (Astrand et al. 1973; Dallas et al. 1989; Hobara et al. 1982, 1983; Monster et al. 1979; Morgan et al. 1972a, 1972b; Nolan et al. 1984), the skin (Fukabori et al. 1977; Morgan et al. 1991; Riihimaki and Pfaffli 1978; Stewart and Dodd 1964; Tsuruta 1975) and the gastrointestinal tract (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). The lipophilic nature of 1,1,1-trichloroethane, the rates of

absorption upon various routes of exposure, and the rates at which the chemical leaves the body in expired air when exposure is terminated all suggest that 1,1,1-trichloroethane is very likely transported across cellular membranes by passive diffusion.

No known specific intermediary molecules influence the distribution of 1,1,1-trichloroethane among tissues in the body. The lipophilicity and volatility of 1,1,1-trichloroethane, along with the low rates at which it is metabolized, appear to be the most important factors influencing distribution within and elimination from the body. The compound is widely distributed by the blood among tissues, with preferential accumulation in fatty tissues, and is rapidly cleared following exposure cessation (Holmberg et al. 1977; RTI 1987; Schumann et al. 1982a, 1982b; Takahara 1986b).

The mechanism by which high levels of 1,1,1-trichloroethane produces mild to moderate hepatotoxic effects in humans and animals is only partially understood. Studies of more potent hepatotoxic chlorinated alkanes (including carbon tetrachloride, chloroform, and 1,1,1-trichloroethane) have clearly demonstrated an involvement of cytochrome P-450-mediated dechlorination in the production of liver injury (Plaa 1986). It has been hypothesized that the production of free radicals via the homolytic cleavage of the carbon-chlorine bond in these hepatotoxic chlorinated alkanes occurs in the endoplasmic reticulum of hepatocytes, and that the free radicals react with unsaturated lipids and proteins in the endoplasmic reticulum, producing lipid peroxidation and covalent binding. These actions lead to morphological and functional changes in this organelle and, eventually, to cellular dysfunction (triglyceride accumulation) and necrosis (Plaa 1986). The potency of the 1,1,2- isomer of trichloroethane to produce liver injury is markedly greater than that of the 1,1,1- isomer (Carlson 1973; Takahara 1986~). This difference has been associated with differences in the metabolic activation of the two isomers. 1,1,2-Trichloroethane is metabolized to a much greater extent in mice and rats after gavage administration than is 1,1,1-trichloroethane. Urinary excretion of metabolites accounted for >70% of the administered doses of the 1,1,2- isomer; in contrast, >85% of the administered 1,1,1- isomer dose was excreted unchanged in expired air (Mitoma et al. 1985). In experiments with rat liver microsomes, Van Dyke and Wineman (1971) observed that 9.8% of the chloride was enzymatically removed from the 1,1,2- isomer, compared with <0.5% removal of chloride from the 1,1,1- isomer in the same period. The difference in extent of metabolism of the 1,1,2- and 1,1,1- isomers explains the difference in hepatotoxicity of the two compounds (i.e., the 1,1,2- isomer is more potent because greater quantities of reactive metabolites are produced from it); however, whether the mild hepatotoxicity of 1,1,1-trichloroethane is mediated by a metabolite or by the compound itself

is unclear. Carlson (1973) reported that rats pretreated with phenobarbital displayed signs of liver injury (increased levels of SGPT and SGOT and decreased activity of glucose-6-phosphatase) immediately following a 2-hour exposure to 11,600 ppm 1,1,1-trichloroethane; these signs were not apparent in nonpretreated rats exposed to the same 1,1,1-trichloroethane concentration or in rats that had received only the phenobarbital pretreatment. This suggests that metabolic activation is involved in the expression of 1,1,1-trichloroethane's hepatotoxicity. Another study, however, did not find that phenobarbital pretreatment potentiated the hepatotoxicity of 1,1,1-trichloroethane (Cornish et al. 1973).

Acute exposures to high 1,1,1-trichloroethane concentrations can cause sudden death in humans due to ventricular fibrillation, myocardial depression, or respiratory arrest. Animal studies show that arrhythmias (that can lead to ventricular fibrillation) can be produced by exogenously administered epinephrine during or immediately after inhalation exposure to 1,1,1-trichloroethane (Carlson 198 1; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). 1,1,1-Trichloroethane is one of the most potent arrhythmogenic of the volatile organic compounds. The studies indicate that the arrhythmias are not caused directly by 1,1,1-trichloroethane, but result from its sensitization of the heart to epinephrine. The basis for the sensitization is not completely understood, but evidence suggests that the sensitization is produced by 1,1,1-trichloroethane itself and not by its metabolites. Carlson (1981) reported that pretreatment of rabbits with phenobarbital (thereby increasing 1,1,1-trichloroethane metabolism) did not increase the incidence of epinephrine-induced arrhythmias during l-hour exposures to 5,600 ppm, and that treatment with cytochrome P-450 inhibitors (SKP-525A and Lilly 18947) (decreasing the metabolism of 1,1,1-trichloroethane) 30 minutes before exposure to 1,1,1-trichloroethane increased the incidence of epinephrine-induced cardiac arrhythmias. The arrhythmogenicity of 1,1,1-trichloroethane and other halogenated hydrocarbons may involve intercellular communication inhibition, presumably through parent-compound modification of gap junctions between cardiac myocytes. Toraason et al. (1992) demonstrated that a series of halogenated hydrocarbons, including 1,1,1-trichloroethane, inhibited the transfer of a fluorescent probe between adjacent cultured cardiac myocytes isolated from neonatal rats (an assay for gap junction communication) and that the inhibition was not affected by pretreating the cells with SKF-525A. Toraason et al. (1992) noted that the ability of the compounds to inhibit intercellular communication paralleled their ability to sensitize the heart to epinephrine-induced arrhythmias.

Acute exposure to high concentrations of 1,1,1-trichloroethane (≈10,00-26,000 ppm) lowered blood pressure in humans and animals within minutes of exposure (Herd et al. 1974; Kobayashi et al. 1988;

McLeod et al. 1987; Wright and Strobl 1984). Studies with anesthetized dogs associated the decrease in blood pressure with peripheral vasodilation at the lower end of the effective concentration range and with decreased heart rate and myocardial contractility at higher concentrations (Herd et al. 1974; Kobayashi et al. 1988). Intravenous administration of phenylephrine (an agent that putatively constricts peripheral vasculature) or calcium counteracted the blood pressure-reducing effects of 1,1,1-trichloroethane in anesthetized dogs (Herd et al. 1974). Herd et al. (1974) hypothesized that 1,1,1-trichloroethane, because of its lipophilic nature, may produce cardiotoxic effects through an interference with membrane-dependent processes such as adenosine triphosphate (ATP) production by cardiac mitochondria and calcium mobilization during myocardial contraction. More recently, Toraason et al. (1990) demonstrated a reversible, concentration-dependent inhibitory effect of 1,1,1-trichloroethane on the contractility (i.e., decreased beating frequency) of cultured rat heart cells. Hoffman et al. (1992) showed that 1,1,1-trichloroethane inhibits calcium mobilization during excitation-contraction coupling in isolated ventricular myocytes from rat neonates, and hypothesized that myocardial depression following exposure to 1,1,1-trichloroethane results from reduced intracellular calcium concentration during systole.

Respiratory arrest due to central nervous system depression has been proposed as a possible explanation for sudden deaths following acute exposure to high concentrations of 1,1,1-trichloroethane (Adams et al. 1950; Jones and Winter 1983; Torkelson et al. 1958). In general, the actions of 1,1,1-trichloroethane are very similar to other central nervous system depressants. The mechanism by which acute exposures to high concentrations of 1,1,1-trichloroethane depress the central nervous system is poorly understood, but is thought to involve interactions or the mere presence of the compound with lipids and/or proteins in neural membranes that lead to dysfunction (Evans and Balster 1991). In support of the hypothesis that the central nervous system depressive effect of 1,1,1-trichloroethane and other organic solvents may be due to interactions with proteinaceous components of membranes, Korpela (1989) demonstrated that 1,1,1-trichloroethane (and other organic solvents) inhibited the activities of membrane-bound integral enzymes (acetylcholinesterase and magnesium-activated ATPase) in synaptosomes isolated from rat cerebrum.

2.4 RELEVANCE TO PUBLIC HEALTH

Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Deaths of persons exposed to high concentrations have been attributed to cardiac arrhythmia and respiratory failure secondary to central nervous system depression. Mild developmental effects observed in animals at high levels have not been verified in humans. Animal studies suggest that exposure to 1,1,1-trichloroethane is not likely to cause reproductive effects or cancer. In general, route of exposure does not appear to be as important as circulating levels of 1,1,1-trichloroethane. Overall, it does not appear that exposures likely to occur near NPL hazardous waste sites are likely to have a deleterious effect on the public's health.

Minimal Risk Levels for 1,1,1-Trichloroethane

Inhalation MRLs

- An MRL of 2 ppm has been derived for acute inhalation exposure (14 days or less) to 1,1,1-trichloroethane.

The acute inhalation MRL is based on a LOAEL of 175 ppm for reduced performance of psychomotor tests in a human study by Mackay et al. (1987). Individuals exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours demonstrated impaired performance of psychomotor tests. The derivation of this MRL is supported by the study results of Gamberale and Hultengren (1973), who also found psychophysiological test performance deficits in exposed individuals, although at a higher concentration, and by numerous studies showing behavioral and neurophysiological effects in animals.

- An MRL of 0.7 ppm has been derived for intermediate inhalation exposure (15-364 days) to 1,1,1-trichloroethane.

The intermediate inhalation MRL is based on a NOAEL of 70 ppm derived from the study by Rosengren et al. (1985) which found evidence of astrogliosis (increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months. Choice of a neurological end point for derivation of the MRL is supported

by numerous studies in humans and animals showing neurological effects to be the critical end point for 1,1,1-trichloroethane.

A chronic inhalation MRL was not derived because suitable studies including tests for subtle neurological effects were not available.

Oral MRLs

Oral MRLs were not derived for 1,1,1-trichloroethane due to the lack of adequate studies. Unpublished studies by Bruckner (1983), which were initially considered as potential candidates for derivation of acute- and intermediate-duration oral MRLs, were peer-reviewed and found to be of inadequate design. A similar conclusion was found regarding a chronic-duration oral study by Maltoni et al. (1986).

Death. The volatility of 1,1,1-trichloroethane, in addition to the rapid and extensive absorption and elimination of the inhaled compound, makes acute inhalation in product use situations the most likely lethal exposure scenario in humans. The acute lethal air concentration for humans is unknown; however, simulations of several lethal exposures suggest that it may be as low as 6,000 ppm (Droz et al. 1982; Jones and Winter 1983; Silverstein 1983). The results of animal studies indicate that the acute lethal exposure concentration decreases substantially with increasing exposure duration. Thus, the concentration required to cause animal death after a 6-7-hour exposure is 3-4 times less than that required after a 15-minute exposure (Adams et al. 1950; Bonnet et al. 1980; Clark and Tinston 1982; Gradiski et al. 1978).

Human deaths after inhalation exposure to 1,1,1-trichloroethane have been attributed to respiratory failure secondary to central nervous system depression and to cardiac arrhythmias (Guberan et al. 1976; Hall and Hine 1966; Jones and Winter 1983; MacDougaJl et al. 1987; Stahl et al. 1969; Travers 1974). Animal studies reveal that arrhythmias may result from sensitization of the heart to epinephrine (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973). Hypoxia may exacerbate the situation (Reinhardt et al. 1971). Therefore, acute lethal exposure levels may be lower in individuals exposed during physical exertion (King et al. 1985; Ranson and Berry 1986; Troutman 1988). Physical exertion also may decrease the acute lethal exposure level by increasing the respiratory rate and lung perfusion rate, thereby increasing the systemic absorption of 1,1,1-trichloroethane.

Very little is known about the lethality of ingested 1,1,1-trichloroethane in humans. In one case of acute oral exposure, accidental ingestion of 600 mg/kg of 1,1,1-trichloroethane was not fatal (Stewart and Andrews 1966). Animal studies suggest that even higher acute oral doses may not cause death. (Kinkead and Wolfe 1992; Torkelson et al. 1958).

Human deaths involving dermal exposure to 1,1,1-trichloroethane have not been reported. Such an occurrence is extremely unlikely in view of the high volatility of 1,1,1-trichloroethane, which would limit the amount of 1,1,1-trichloroethane in contact with the skin, and the relatively slow rate of percutaneous absorption. Animal deaths were observed only when extremely high doses (15,800 mg/kg) were applied to the skin for prolonged periods (e.g., 24 hours) under occlusive dressings (Torkelson et al. 1958).

Systemic Effects.

Respiratory Effects. Respiratory depression produced by 1,1,1-trichloroethane is considered secondary to central nervous system depression. See the discussion of Neurological Effects for more information.

Cardiovascular Effects. 1,1,1-Trichloroethane can lower blood pressure (mildly to severely) in humans (Domette and Jones 1960; Krantz et al. 1959) and can induce transient myocardial injury (Wodka and Jeong 1991). Such effects, however, are likely only after exposure to very high concentrations of 1,1,1-trichloroethane vapor. Daily exposure to low levels for 16 years did not affect blood pressure, heart rate, or electrocardiogram results in humans (Kramer et al. 1978). Reduced blood pressure accompanies exposure to anesthetic concentrations of 1,1,1-trichloroethane vapor (10,000-26,000 ppm). The effects are not permanent and subside shortly after exposure. The hypotensive mechanism has been studied in animals and appears to involve cardiac depression and peripheral vasodilation (Herd et al. 1974).

Human deaths following 1,1,1-trichloroethane inhalation are often attributed to cardiac arrhythmias (Guberan et al. 1976; MacDougall et al. 1987; Travers 1974). Such conclusions are based on animal studies in which arrhythmias have been produced during or immediately following acute inhalation exposure to 1,1,1-trichloroethane (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973; Trochimowicz et al. 1974). The mechanism for the arrhythmias apparently involves sensitization of the heart to endogenous epinephrine. The exposure level at which cardiac sensitization occurs in

humans is not known, but in animals, concentrations as low as 5,000 ppm are effective after only 10 minutes of inhalation (Reinhardt et al. 1973). Physical exertion, stress, or any other stimulus of epinephrine release from the adrenal medulla may render an individual more vulnerable to 1,1,1-trichloroethane. Hypoxia may further increase a subject's susceptibility.

Gastrointestinal Effects. Nausea, vomiting, and diarrhea reportedly occur in humans after acute oral or inhalation exposure to high 1,1,1-trichloroethane levels (Jones and Winter 1983; McCarthy and Jones 1983; Stewart 1971; Stewart and Andrews 1966). Vomiting and diarrhea have not been reported in animals (rodents, the most commonly used laboratory animals, cannot vomit). The mechanisms for these effects are not known.

Hepatic Effects. 1,1,1-Trichloroethane may be a mild hepatotoxin in humans, although the evidence is not conclusive. Increased levels of serum bilirubin, LDH, alkaline phosphatase and SGOT, all suggestive of liver injury, have been reported in humans exposed to high levels of 1,1,1-trichloroethane by inhalation or ingestion (Halevy et al. 1980; Hodgson et al. 1989; Stewart and Andrews 1966). Mild hepatic changes have also been found by liver biopsy in exposed individuals and at autopsy in individuals who died after acute inhalation exposure to high concentrations of 1,1,1-trichloroethane (Caplan et al. 1976; Halevy et al. 1980; Hall and Hine 1966; Hodgson et al. 1989). Animals studies indicate that exposure to relatively high 1 ,l ,l -trichloroethane concentrations in air (≥1,000 ppm) or high oral doses (≥1,334 mg/kg) are required to produce liver injury (Adams et al. 19.50; Bruckner 1983; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958; Tyson et al. 1983). Effects observed in animals include necrosis, fatty change, increased liver weight, and changes in liver and serum enzyme levels. These effects are reversible and subside after termination of exposure (in the case of necrosis, hepatocytes in the proximity of the killed cells proliferate and replace them).

Dermal Effects. 1,1,1-Trichloroethane is mildly irritating when applied undiluted to the skin for extended periods (Duprat et al. 1976; Stewart and Dodd 1964; Torkelson et al. 1958; Wahlberg 1984a, 1984b). Effects include slight, transient, reversible erythema and edema. Low concentrations in water, however, are not likely to cause skin irritation when bathing or showering.

Ocular Effects- Exposure to high levels of 1,1,1-trichloroethane vapor is associated with mild eye irritation in humans (Stewart et al. 1961) and mice (Evans and Balster 1993). Tests in animals suggest

that 1 ,l ,l -trichloroethane applied directly to the eye is likely to cause only mild eye irritation in humans (Duprat et al. 1976; Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958).

Immunological and Lymphoreticular Effects. Immunological effects of 1,1,1-trichloroethane have not been reported in humans, other than one case of dermal sensitization (Ingber 1991) and have not been studied extensively in animals. Spleen congestion has been observed in subjects who were accidentally exposed to 1,1,1-trichloroethane at a high concentration (Gresham and Treip 1983; Stahl et al. 1969); however, this effect may have been due to altered peripheral hemodynamics. Acute inhalation exposure had no effect on survival from a bacterial pathogen challenge in mice (Aranyi et al. 1986). Histological evaluation of lymphoreticular tissues from rats and mice (including lymph nodes, thymus, and spleen) have not revealed any lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Comish and Adefuin 1966; Kjellstrand et al. 1985b; Prendergast et al. 1967; Torkelson et al. 1958); however, more extensive immune function studies would be required to adequately evaluate the immunotoxic potential of 1,1,1-trichloroethane in humans.

Neurological Effects. Neurological effects are the preeminent signs of acute inhalation exposure to 1,1,1-trichloroethane in humans. The intoxicating effects of the inhaled chemical create a potential for its abuse. The severity of CNS depressant effects in humans during acute inhalation exposure increases as the exposure duration and level are increased. Impaired performance of psychophysiological function tests has been observed in individuals exposed to moderate concentrations (≥175 ppm) (Gamberale and Hultengren 1973; Mackay et al. 1987). The Mackay et al. (1987) study served as the basis for the acute-duration inhalation MRL. Dizziness, lightheadedness, and loss of coordination are caused by exposure to higher concentrations (>500 ppm) (Stewart et al. 1961, 1969; Torkelson et al. 1958). General anesthesia occurs at high levels (≥10,000 ppm) (Domette and Jones 1960). These effects subside rapidly after exposure. A recent report suggested that impaired memory and deficits in balance were persistent effects in a group of workers after chronic exposure to moderate to high levels of 1,1,1-trichloroethane (Kelafant et al. 1994). This population is being followed-up to determine the validity of these new findings.

Animals are useful models for examining the neurological effects of exposure to 1,1,1-trichloroethane. As in humans, central nervous system depression is the predominant effect of inhaled 1,1,1-trichloroethane. Signs include ataxia, unconsciousness, and death at increasing concentrations (Bonnet et al.

1980; Clark and Tinston 1982; Evans and Balster 1993; Gehring 1968; Hougaard et al. 1984; Lazarew 1929). No evidence of gross or histological damage was found in the brains of most exposed animals, but lasting physical changes in the brain are indicated by reports of increased levels of glial fibrillary acid protein and decreased DNA content in the brain of gerbils after intermediate exposure to low levels of the chemical (Karlsson et al. 1987; Rosengren et al. 1985). The Rosengren et al. (1985) study served as the basis for the intermediate-duration inhalation MRL. Alterations of brain metabolism also were observed in exposed animals (Folbergrova et al. 1984; Hougaard et al. 1984; Nilsson 1986a, 1986b). Behavioral changes, including impaired performance of neurobehavioral tests and increased motor activity, have been widely reported (Albee et al. 1990a; Balster et al. 1982; DeCeaurriz et al. 1983; Geller et al. 1982; Horiguchi and Horiguchi 1971; Kjellstrand et al. 1985a; Mattsson et al. 1993; Moser and Balster 1985, 1986; Moser et al. 1985; Mullin and Krivanek 1982; Woolverton and Balster 1981); however, the sites of action and biochemical mechanisms of neurotoxicity have not been identified. Neurophysiological changes also have been reported (Albee et al. 1990b). These latter observations were made at relatively high exposure levels.

Little information was located regarding neurological effects in humans or animals after oral or dermal exposure to 1,1,1-trichloroethane. Existing data indicate that a single oral exposure to a dose of approximately 600 mg/kg did not produce overt signs of neurotoxicity (Stewart and Andrews 1966). It is assumed, however, that sufficiently high doses of 1,1,1-trichloroethane administered orally or dermally will result in neurological effects. Oral exposure to 1,1,1-trichloroethane produced neurophysiological changes in rats given moderate doses (700 mg/kg/day) (Spencer et al. 1990), and in gross neurobehavioral changes (hyperexcitability and narcosis) in rats given high doses (5,000 mg/kg/day) (Bruckner 1983). No neurological effects were observed in the offspring of rats treated by gavage during gestation and lactation with up to 750 mg 1,1,1-trichloroethane/kg/day (Dow Chemical 1993) (see Developmental Effects).

Reproductive Effects. Adverse effects of 1,1,1-trichloroethane on reproduction in humans have not been reported. Taskinen et al. (1989) found no relationship between adverse pregnancy outcomes and exposure of fathers to 1 ,l ,l-trichloroethane during spermatogenesis. Histological evaluation of reproductive organs and tissues from rats and mice of either sex revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was

observed in guinea pigs (Adams et al. 1950). More extensive and sensitive tests are required before the potential for human reproductive effects can be fully evaluated.

Developmental Effects. Developmental effects in humans exposed to 1,1,1-trichloroethane have not been observed. Epidemiology studies found no relationship between adverse pregnancy outcomes and maternal exposure to 1,1,1-trichloroethane (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Minor embryotoxic effects were observed in rats and rabbits after inhalation exposure to high concentrations of 1,1,1-trichloroethane (BRRC 1987a, 1987b; York et al. 1982). Effects included decreased fetal weights, increased minor soft tissue and skeletal anomalies, and delayed ossification. The developmental defects reported in two of these studies (BRRC 1987a, 1987b) may have been associated with significant maternal toxicity. Neither an inhalation study using a lower, although still high, concentration (Schwetz et al. 1975) nor drinking water studies (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b) revealed any developmental effects. Furthermore, a recent comprehensive study in which pregnant rats were gavaged with 1,1,1-trichloroethane during gestation and lactation found no neurobehavioral alterations in the pups tested up to 2 months of age (Dow Chemical 1993). Overall, 1,1,1-trichloroethane does not appear to be a significant developmental toxicant in animals. However, in view of the known neurological effects of 1,1,1-trichloroethane in humans and animals, additional developmental studies that examine neurological end points would be an important component of a complete investigation of 1,1,1-trichloroethane's potential developmental toxicity in humans.

Genotoxic Effects. The genotoxic effects of 1,1,1-trichloroethane have been studied ,extensively . The results are summarized in Tables 2-4 and 2-5. Although most tests of mutagenicity in the Ames *Salmonella* assay produced negative results, those conducted in a desiccator, to minimize evaporation and maximize exposure, were mostly positive (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results indicate that 1,1,1-trichloroethane may be mutagenic in *Salmonella. The* results were negative in other tests of genotoxicity in bacteria and fungi. 1,1,1-Trichloroethane is a relatively volatile compound; therefore, a high evaporation rate could result in lower doses reaching the microorganisms and thus affect the outcome of genotoxicity tests. This explanation may account for the largely negative results observed in tests with bacteria and fungi. On the other hand, many compounds more volatile than 1,1,1-trichloroethane are positive in these studies.

TABLE 2-4. Genotoxicity of 1,1,1-Trichloroethane *In Vivo*

Species (test system)	End point	Results	Reference
Tradescantia	Pigmentation change in plant stamen hairs	+	Schairer et al. 1983
Drosophila melanogaster	Sex linked recessive lethal mutations	–	Gocke et al. 1981
Mouse erythrocytes	Micronucleus test	–	Tsuchimoto and Matter 1981
Mouse bone marrow	Micronucleus test	–	Gocke et al. 1981; Katz et al. 1981; Mackay 1990; Salamone et al. 1981
Mouse liver	DNA adducts	(+)	Turina et al. 1986
Mouse liver	DNA unwinding	–	Taningher et al. 1991

– = negative; + = positive; (+) = weakly positive; DNA = deoxyribonucleic acid

TABLE 2-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium on plates	Reverse mutation	–	–	Baker and Bonin 1981; Brooks and Dean 1981; Ichinotsubo et al. 1981; MacDonald 1981; Martire et al. 1981; Mersch-Sundermann 1989; Nagao and Takahashi 1981; Nestmann et al. 1980; Quillardet et al. 1985; Richold and Jones 1981; Rowland and Severn 1981; Simmon and Shepherd 1981; Trueman 1981; Venitt and Crofton-Sleigh 1981
S. typhimurium in liquid	Reverse mutation	–	–	Falck et al. 1985; Suovaniemi et al. 1985
S. typhimurium on plates in dessicator	Reverse mutation	+	+	Nestmann et al. 1980, 1984; Gocke et al. 1981; Simmon et al. 1977
		–	–	Milman et al. 1988
S. typhimurium	Fluctuation	–	–	Gatehouse 1981; Hubbard et al. 1981
S. typhimurium	Forward mutation	–	No data	Skopek et al. 1981
		–	–	Roldan-Arjona et al. 1991
S. typhimurium	*umu*-test	–	–	Nakamura et al. 1987; Ono et al. 1991a, 1991b
	Rec-assay for DNA repair	–	–	Kada 1981
Escherichia coli	Reverse mutation	–	–	Matsushima et al. 1981
E. coli	Differential killing	–	–	Green 1981; Tweats 1981
E. coli	Lambda prophage induction	–	–	Thomson 1981
E. coli	Gene induction	–	No data	Quillardet et al. 1985
E. coli	Growth inhibition	(+)	–	Rosenkranz et al. 1981

TABLE 2-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Eukaryotic organisms:				
Fungi:				
Schizosaccharomyces pombe	Forward mutation	–	–	Loprieno 1981
Aspergillus nidulans	Forward mutation	No data	–	Crebelli and Carere 1987
A. nidulans	Mitotic aneuploidy	No data	–	Cerebelli and Carere 1987; Crebelli et al. 1988
A. nidulans	Mitotic crossing over	No data	–	Crebelli and Carere 1987
Saccharomyces cerevisiae	Reversion	–	–	Mehta and von Borstel 1981
S. cerevisiae	Mitotic aneuploidy	No data	–	Whittaker et al. 1990
		–	No data	Parry and Sharp 1981
S. cerevisiae	Mitotic crossing over	–	–	Kassinova et al. 1981
S. cerevisiae	DNA repair	–	–	Sharp and Parry 1981a
S. cerevisiae	Mitotic gene conversion	–	–	Sharp and Parry 1981b; Jagannath et al. 1981; Zimmerman and Scheel 1981
Mammalian cells:				
HeLa cells	Unscheduled DNA synthesis	–	–	Martin and McDermid 1981
Mouse hepatocytes	Unscheduled DNA synthesis	No data	+	Milman et al. 1988
Rat hepatocytes	Unscheduled DNA synthesis	No data	–	Althaus et al. 1982; Milman et al.1988; Shimada et al. 1985; Williams et al. 1989

TABLE 2-5. Genotoxicity of 1,1,1-Trichloroethane *In Vitro* (continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Rat hepatocytes	Degranulation of endoplasmic reticulum	No data	+	Fey et al. 1981
Human lymphoblasts	Gene locus mutation	No data	–	Penman and Crespi 1987
L5178Y mouse lymphoma cells	Forward mutation	?	–	Myhr and Caspary 1988
		–	–	Mitchell et al. 1988
Chinese hamster ovary cells	Chromosome aberrations	(+)	+	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	–		Perry and Thomson 1981
		?	–	Galloway et al. 1987
Human peripheral lymphocytes	Sister chromatid exchange	No data	–	Lindahl-Kiessling et al. 1989
Baby hamster kidney cells	Cell transformation	–	No data	Styles 1981
		+	+	Daniel and Dehnel 1981
Rat embryo cells F1706	Cell transformation	No data	+	Price et al. 1978
Hamster embryo cells	Cell transformation	No data	+	Hatch et al. 1982, 1983
Mice BALB/c-3T3 cells	Cell transformation	No data	+	Tu et al. 1985; Milman et al. 1988
Calf thymus	Binding to DNA	–	No data	DiRenzo et al. 1982

– = negative; + = positive; (+) = weakly positive; ? = equivocal; DNA = deoxyribonucleic acid

Most assays of genotoxicity in mammalian cells have been negative, but 1,1,1-trichloroethane did produce chromosomal aberrations in Chinese hamster ovary cells *in vitro* (Galloway et al. 1987). *In vivo* micronucleus tests for chromosomal aberrations were all negative (Gocke et al. 1981; Katz et al. 1981; Mackay 1990; Salamone et al. 1981; Tsuchimoto and Matter 1981). Positive or weakly positive results were reported in assays for unscheduled DNA synthesis in mouse hepatocytes (Milman et al. 1988); degranulation of endoplasmic reticulum, which measures the ability of a compound to displace polysomes from endoplasmic reticulum in rat hepatocytes *in vitro* (Fey et al. 1981); and formation of DNA adducts (binding of the compound to DNA) in mouse liver *in vivo* (Turina et al. 1986). Tests of cell transformation in rat embryo cells, hamster embryo cells, baby hamster kidney cells, and mouse BALB/c-3T3 cells were almost all positive (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Cell transformation systems are believed to be similar to the process of neoplastic transformations.

Although 1,1,1-trichloroethane was mutagenic in a few assays with *Salmonella,* induced chromosomal aberrations in a Chinese hamster ovary cell assay, and was positive in most mammalian cell transformation assays, the existing genotoxicity data are largely negative. In addition, positive results may have been produced by stabilizers and not 1,1,1-trichloroethane itself. Therefore, a firm conclusion regarding the genotoxic potential of 1,1,1-trichloroethane in humans is not possible.

Cancer. A relationship between exposure to 1,1,1-trichloroethane and cancer in humans has not been established. Among animals, no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988). The results of an oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats; however, the biological and statistical significance of these results are questionable because of the study design limitations (Maltoni et al. 1986). The results of another oral (gavage) cancer bioassay (NCI 1977) were negative, but high early mortality in treated animals in this study made these results questionable.

Information is also limited on the role of 1,1,1-trichloroethane metabolites in the compound's toxicity. Reactive metabolites are important in the carcinogenicity of other chloroethanes (i.e., 1,1,2,2-tetrachloroethane). Binding to DNA, which is correlated with carcinogenicity in chlorinated ethanes (Lattanzi et al. 1988), was weak in an *in vivo* test (Turina et al. 1986). Even weak binding, however, indicates the potential to interact with DNA. Cell biotransformation tests were positive for

this chemical (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). The results of these assays may have been confounded by the presence of stabilizing agents, however. Two of the common stabilizing additives in commercial formulations of 1,1,1-trichloroethane are 1,2-epoxybutane (butylene oxide), and 1,4-dioxane (diethylene dioxide). Both stabilizers have been identified as animal carcinogens (NTP 1989a). At this time, it does not appear that 1,1,1-trichloroethane exposure poses a clear cancer risk in animals; however, as discussed above, the limitations of the available studies prevent a definitive assessment of the risk of cancer in humans exposed to the compound. Related to potential exposures near NPL hazardous waste sites, the risk appears to be of little significance.

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,1,1-trichloroethane are discussed in Section 2.5.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals

of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,1,1-trichloroethane are discussed in Section 2.5.2.

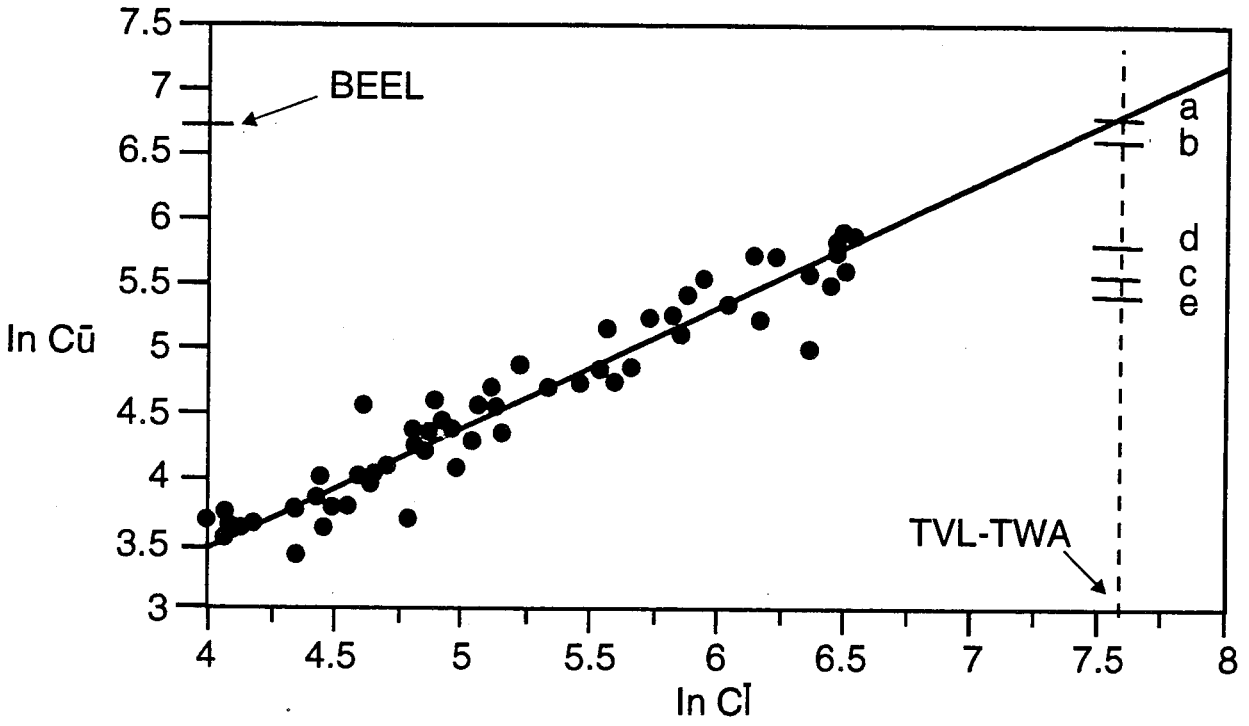
A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, Populations That Are Unusually Susceptible.

2.5.1 Biomarkers Used to Identify or Quantify Exposure to 1,1,1-Trichloroethane

Environmental levels of 1,1,1-trichloroethane have been correlated with levels in expired air, blood, and urine. After extensive studies, a significant correlation was observed between the environmental exposure of humans to 1,1,1-trichloroethane and levels of the chemical in expired air in various United States locations during various seasons (Hartwell et al. 1987a; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987c). Levels of 1,1,1-trichloroethane and its metabolites, trichloroethanol and trichloroacetic acid, have been quantified in the blood, expired air, and urine of workers exposed to 50 ppm 1,1,1-trichloroethane for 1 week (Monster 1986). Immediately following exposure, urine levels of trichloroethane and trichloroacetic acid were 4.9 and 2.5 mg/g creatinine, respectively. At 5-15 minutes after exposure, 1,1,1-trichloroethane levels in the blood and expired air were 0.9 mg/L and 210 mg/m^3, respectively. The blood levels of trichloroethanol and trichloroacetic acid were 0.16 and 2.3 mg/L, respectively. For comparison, the baseline level of 1,1,1-trichloroethane in the blood of unexposed, normal subjects was 0.0002 mg/L (range <0.0001-0.0034 mg/L), and the blood level of trichloroacetic acid was 0.0214 mg/L (Hajimiragha et al. 1986).

Studies of 1,1,1-trichloroethane levels in expired air or its metabolites in the urine have established a linear correlation between urinary trichloroethanol concentrations and environmental 1,1,1-trichloroethane levels or 1,1,1-trichloroethane levels absorbed through the lungs (Ghittori et al. 1987; Imbriani et al. 1988; Monster 1986; Pezzagno et al. 1986; Seki et al. 1975; Stewart et al. 1961). Data from Imbriani et al. (1988) are presented in Figure 2-4. Monster (1986) proposed that the best method for

Figure 2-4. Scatter Diagram Relating Time-Weighted Average of Environmental Concentration and Urinary Concentration of 1,1,1-Trichloroethane in Exposed Workers



Scatter diagram relating the time-weighted average of the environmental concentration (in the breathing zone) (C̄I) and the urinary concentration (Cū) of 1,1,1-trichloroethane in the exposed workers (experiment II). The regression line (Cū=0.45xCI+12.6; r=0.95; N=60) is also drawn.
a Cū value at C̄I = 1,900 mg/m^3 (TLV-TWA)
b 95% lower confidence limit = biological exposure limit
c hypothetical value of Cū in an occupationally exposed subject
d one-sided upper confidence limit (at 95%) of Cū
e one-sided lower confidence limit (at 95%) of Cū

Classification system:
1 d<b (or d/b<1) = compliance exposure
2 e>b (or e/b>1) = noncompliance exposure
3 any individual which cannot be classified in 1 or 2 = possible overexposure

The C̄I and Cū values are shown as 1n numbers to allow all the data in a same diagram. The TVL-TWA is 19,900 mg/m^3 (anti-1n 7.549).
The BEEL is 805 μ/L (anti-1n 6.690)

Taken from Imbriani et al. 1988

estimating occupational exposure to I ,l,l-trichloroethane was to determine the levels of 1,1,1-trichloroethane and trichloroacetic acid in blood after work on Fridays.

The length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air (Monster et al. 1979; Morgan et al. 1970, 1972b; Nolan et al. 1984; Stewart et al. 1961, 1969). Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid. Furthermore, 1,1,1-trichloroethane is rapidly eliminated from the body; ≥99% is eliminated within 50 hours (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). See Section 2.3 for more information regarding the pharmacokinetics of 1,1,1-trichloroethane. The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene (Monster 1988). If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,1,1-Trichloroethane

The central, nervous system is apparently the most sensitive tissue to 1,1,1-trichloroethane exposure. Decreased psychomotor performance, altered EEG recordings, ataxia, and anesthesia have been observed in humans after acute exposure (Domette and Jones 1960; Mackay et al. 1987; Stewart et al. 1975; Torkelson et al. 1958). Mild hepatic effects and decreased blood pressure have also been noted (Domette and Jones 1960; Stewart et al. 1961). Numerous animal studies provide supporting evidence for the sensitivity of the central nervous system to acute and intermediate-duration exposure to 1,1,1-trichloroethane. Adverse cardiovascular effects and mild hepatic effects have also been observed in animals. Indices of central nervous system, hepatic, and cardiovascular effects are of limited value, as biomarkers, since many other lipophilic chemicals (including some likely to be present at the same sites as 1,1,1-trichloroethane) may cause similar effects in these target organs.

No specific biomarkers of effects caused by 1,1,1-trichloroethane were found in the literature. Additional information regarding the effects of exposure to 1,1,1-trichloroethane can be found in OTA (1990) and CDC/ATSDR (1990). For a more detailed discussion of the health effects caused by 1,1,1-trichloroethane see Section 2.2 of Chapter 2.

2.6 INTERACTIONS WITH OTHER SUBSTANCES

Although there are no reports of chemical interactions in humans, several animal studies have identified possible interactions between 1,1,1-trichloroethane and other chemicals.

Ethanol, when given orally to mice at doses of 0.125-2.0 g/kg, potentiated both the lethality and behavioral effects (inverted screen test) of inhaled 1,1,1-trichloroethane at concentrations ranging from ≈200 to 10,000 ppm (Woolverton and Balster 1981). In another study, a 3-day pretreatment of mice with ethanol enhanced 1,1,1-trichloroethane-induced liver toxicity, as indicated by an assay of liver function (bromosulfophthalein retention in plasma), but not an assay of liver damage (SGPT levels) (Klaassen and Plaa 1966). Other studies, using only serum enzyme levels to assay liver damage (SGPT or SGOT), found that ethanol markedly and consistently enhanced the hepatotoxicity of more potent chlorinated compounds such as carbon tetrachloride or trichloroethylene, but had no effect on the hepatotoxicity of 1,1,1-trichloroethane (Comish and Adefuin 1966; Klaassen and Plaa 1967). Ethanol may potentiate the hepatotoxicity of chlorinated alkanes because of its ability to induce cytochrome P450IIEl (Ikatsu and Nakajima 1992). The available data indicate that ethanol can enhance the acute neurobehavioral effects of 1,1,1-trichloroethane, but will not cause 1,1,1-trichloroethane to produce severe liver damage (necrosis) like that caused by other chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane.

Co-exposure of control or ethanol-treated rats to inhaled concentrations of 10 ppm carbon tetrachloride and 200 ppm 1,1,1-trichloroethane did not produce changes in several indices of liver damage (SGPT, SGOT, and liver malondialdehyde) compared with exposure to 10 ppm carbon tetrachloride alone (Ikatsu and Nakajima 1992). This indicates that 1,1,1-trichloroethane may be protective against hepatotoxic effects of cytotoxic haloalkanes. In contrast, co-exposure of ethanol-treated rats to 10 ppm carbon tetrachloride and 10-50 ppm chloroform produced liver damage that was greater than the additive effects of exposure to each component alone; this synergistic interaction was not observed in rats fed a diet without ethanol (Ikatsu and Nakajima 1992). Extrapolation of these results to humans suggests that heavy drinkers exposed to mixtures of carbon tetrachloride and chloroform may have a greater risk of developing liver damage than those exposed to either chlorinated alkane alone. The results, however, provide no evidence for a synergistic interaction between carbon tetrachloride and 1,1,1-trichloroethane that would enhance the hepatotoxicity of either compound. In experiments with

isolated rat hepatocytes, concomitant exposure to chloroform, but not co-exposure to 1,1,1-trichloroethane, potentiated carbon tetrachloride-induced lipid peroxidation (Kefalas and Stacey 1991).

Ketones and ketogenic substances (i.e., substances metabolized to ketones or that produce ketosis in the body) potentiate the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,2-trichloroethane (Plaa 1988). Although the mechanism of this potentiation is not fully understood, Plaa (1988) has proposed enhanced bioactivation of the toxicant through cytochrome P-450 induction. Studies with mice, however, found that treatment with acetone or isopropanol (which is metabolized to acetone) did not enhance the hepatotoxicity of 1,1,1-trichloroethane, but enhanced the threshold doses of chloroform, 1,1,2-trichloroethane, and trichloroethylene to elevate SGPT (Traiger and Plaa 1974). Single intraperitoneal doses of 1,1,1-trichloroethane (1.0 mL/kg) did not produce liver damage (assayed either as elevation in SGPT or in concentrations of liver triglycerides) in control mice or in mice with alloxan-induced diabetes (i.e., that were in a state of ketosis) (Hanasono et al. 1975). Other studies examining the influence of agents that enhance cytochrome P-450 metabolism have provided mixed results. The cytochrome P-450 mixed-function oxidase inducer, phenobarbital, enhanced the hepatotoxicity of 1,1,1-trichloroethane in the rat study by Carlson (1973) but not in that of Cornish et al. (1973). In general, the available data suggest that ketones, ketogenic substances, or cytochrome P-450 inducers will not potentiate 1,1,1-trichloroethane hepatotoxicity.

Concurrent injections of nicotine potentiate the lethality produced by intraperitoneal injection of 1,1,1-trichloroethane in mice (Priestly and Plaa 1976). Although no explanation has been given for the effect of nicotine, stimulation of the sympathetic nervous system and release of epinephrine from the adrenal medulla might enhance cardiac arrhythmias.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to 1,1,1-trichloroethane than will most persons exposed to the same level of 1,1,1-trichloroethane in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the pre-existing

compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.6, Populations With Potentially High Exposure.

Limited data from animal studies (Woolverton and Balster 1981) indicate that alcohol drinkers may be more susceptible to the acute neurobehavioral effects of 1,1,1-trichloroethane. Moderate to heavy alcohol drinkers may be more susceptible to the hepatotoxicity of some chlorinated alkanes, such as carbon tetrachloride, chloroform, and 1,1,1-trichloroethane, due to ethanol induction of hepatic cytochrome P-450 isozymes involved in the activation of these compounds to intermediate hepatotoxic metabolites. Available animal studies (Comish and Adefuin 1966; Klaassen and Plaa 1966, 1967), however, have not demonstrated that ethanol ingestion will potentiate the hepatotoxicity of 1,1,1-trichloroethane. Furthermore, evidence indicates that ethanol does not cause 1,1,1-trichloroethane and carbon tetrachloride to interact synergistically to produce hepatotoxic effects, although such an interaction has been demonstrated for ethanol, carbon tetrachloride, and chloroform (Ikatsu and Nakajima 1992). The available data suggest that alcohol ingestion is not likely to significantly potentiate the hepatotoxicity of 1,1,1-trichloroethane.

Diabetics consistently in a state of ketosis may be more susceptible to the hepatotoxicity of certain chlorinated alkanes including carbon tetrachloride, chloroform, and 1,1,1-trichloroethane, due to a potentiation from increased ketone levels in the body. Animal studies indicate that the ketone potentiation of the hepatotoxicity of chlorinated alkanes involves an enhancement of the metabolic production of hepatotoxic intermediate metabolites. Available data, however, indicate that ketones do not appreciably potentiate the hepatotoxicity of 1,1,1-trichloroethane (Plaa 1986, 1988). Thus, diabetics in a state of ketosis are not likely to be more susceptible to the hepatotoxicity of 1,1,1-trichloroethane than the population at large.

Because 1,1,1 -trichloroethane is associated with some cardiovascular effects (see Section 2.2.1.2), persons with compromised heart conditions may be at additional risk around high exposure levels of 1,1,1-trichloroethane and should be restricted to some lower level of exposure.

Although no data are available that address this issue, it is possible that individuals with impaired respiratory function (e.g., emphysema, poor perfusion) might excrete less 1,1,1-trichloroethane in a given period than other people, since most of a single dose is expired (Monster et al. 1979; Nolan et al. 1984). In situations of prolonged exposure, such as living near a hazardous waste site, this might contribute to accumulation of 1,1,1-trichloroethane in the body. People with respiratory disease might, therefore, constitute a more susceptible population.

Young people might be unusually susceptible to 1,1,1-trichloroethane, since the nervous system continues to develop in humans after birth and this chemical may produce residual neurological effects. Developmental toxicity data in humans are not available to address this question. Neurobehavioral testing of exposed rat pups was negative (York et al. 1982). Although limited animal data did not find evidence to support this idea, it remains possible that children might be more susceptible to 1,1,1-trichloroethane than adults.

2.8 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,1,1-trichloroethane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposure to 1,1,1-trichloroethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.8.1 Reducing Peak Absorption Following Exposure

Ingested 1,1,1-trichloroethane is rapidly absorbed by the gastrointestinal tract of humans and animals (Mitoma et al. 1985; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966). To minimize absorption following ingestion, several treatments have been suggested, including administration of milk or water to dilute the gastrointestinal tract contents, gastric lavage, and the administration of emesis-inducing compounds or activated charcoal (Goldfrank et al. 1990; Stutz and Janusz 1988). Butter or some other food high in lipids might be given. The lipids will serve to delay substantially, and possibly diminish, systemic absorption of the 1,1,1-trichloroethane. It should be noted, however, that upon induction of emesis there is the possibility of aspiration of 1,1,1-trichloroethane into the lungs, which may result in pneumonia. Therefore, treatment via stomach pump has been

recommended. Due to rapid absorption of 1,1,1-trichloroethane by the gut, any measures to retard absorption must be taken very rapidly.

Inhaled 1,1,1-trichloroethane is rapidly absorbed and expired, predominantly unchanged, through the lungs (see Section 2.3.). The rapidity with which inhaled 1,1,1-trichloroethane is absorbed (Astrand et al. 1973; Morgan et al. 1972a, 1972b) indicates that assisted ventilation or positive pressure ventilation techniques will not prevent the absorption of 1,1,1-trichloroethane in the lung and emphasizes the importance of removing the subject from the contaminated atmosphere. Nevertheless, such techniques have been suggested to help eliminate the compound from the body (Bronstein and Currance 1988).

The volatility of 1,1,1-trichloroethane is likely to limit absorption of the dermally applied compound, even though dermal absorption under conditions that prevent evaporation is rapid and extensive (Fukabori et al. 1977; Morgan et al. 1991; Stewart and Dodd 1964; Tsuruta 1975). Washing the skin with soapy water has been suggested to reduce the absorption of dermally applied 1,1,1-trichloroethane (Bronstein and Currance 1988; Goldfrank et al. 1990; Stutz and Janusz 1988). Ethyl or isopropyl alcohol also could be used to dilute 1,1,1-trichloroethane on the skin. Flushing the exposed eye with large quantities of water or saline for 15-30 minutes has been suggested to prevent absorption and soothe irritation (Bronstein and Currance 1988; Stutz and Janusz 1988).

2.8.2 Reducing Body Burden

When exposure to 1,1,1-trichloroethane ceases, regardless of route of exposure, the compound is rapidly cleared from the body, predominantly by exhalation of unchanged 1,1,1-trichloroethane in expired air (see Section 2.3.). Very little metabolism of the compound takes place, and despite a preferential distribution of absorbed 1,1,1-trichloroethane to fatty tissues, significant retention does not occur without continued exposure. Thus, continued ventilation by the lungs will eliminate the compound from the body. Suggested methods to assist in lung ventilation include orotracheal and nasotracheal intubation for airway control and positive pressure ventilation techniques (Bronstein and Currance 1988; Ellenhom and Barceloux 1988).

2.8.3 Interfering with the Mechanism of Action for Toxic Effects

Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane are primarily supportive, rather than active, and are not generally directed against a particular mechanism of action (Bronstein and Currance 1988; Ellenhom and Barceloux 1988; Goldfrank et al. 1990; Herd et al. 1974; Stutz and Janusz 1988). Suggested methods of treatment include removing the subject from the source of exposure, ventilation assistance, gastric dilution and lavage for ingested material, oxygen administration, and skin washing. Continuous cardiac monitoring is routine for exposed patients. These methods rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Mechanisms of action, however, are discussed in this section in relation to the possible development of interfering treatment methods.

The mechanism by which 1,1,1-trichloroethane and other organic solvents depress the central nervous system is poorly understood, but is thought to involve interactions of the parent compound with lipids and/o; proteinaceous components of neural membranes (Evans and Balster 1991). No known methods specifically counteract the central nervous system effects of 1,1,1-trichloroethane. Because the specific cellular or biochemical nature of central nervous system depression is poorly understood, it is difficult to propose any method to interfere with this effect of 1,1,1-trichloroethane, other than to prevent further exposure to the compound so that it can be cleared from the body.

The acute cardiotoxic effects of 1,1,1-trichloroethane (reduced blood pressure and increased sensitization to epinephrine-induced arrhythmias) appear to be mediated by the compound and not its metabolites (Carlson 1973; Toraason et al. 1990, 1992) and have been associated with the ability of 1,1,1-trichloroethane to interfere with membrane-mediated processes including calcium mobilization during myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990) and gap junction communication between myocardial cells (Toraason et al. 1992). The administration of epinephrine to counteract 1,1,1-trichloroethane-induced cardiovascular depression has been cautioned against, because of the risk of arrhythmias and ventricular fibrillation (Bronstein and Currance 1988; Goldfrank et al. 1990; Herd et al. 1974). Herd et al. (1974) demonstrated that intravenous injection or infusion of calcium (as calcium gluconate) or phenylephrine protected against 1,1,1-trichloroethane induced blood pressure reduction in anesthetized dogs and suggested more detailed study to assess whether these compounds could be used routinely to resuscitate exposed individuals. Exogenous calcium appears to counteract the influence of 1,1,1-trichloroethane on calcium mobilization during

myocardial contraction (Herd et al. 1974; Hoffman et al. 1992; Toraason et al. 1990). Evidence indicates that phenylephrine counteracts 1,1,1-trichloroethane-induced vasodilation without influencing myocardial function (Herd et al. 1974). Further studies examining these active methods of treatment were not located.

Unlike more potent chlorinated alkanes such as carbon tetrachloride or 1,1,2-trichloroethane, it is not clear whether the hepatotoxicity of 1,1,1-trichloroethane is due to a metabolite or the parent compound (see Section 2.3.5.). If metabolites produced by cytochrome P-450 oxidation or dechlorination are responsible for the hepatotoxicity, administering cytochrome P-450 inhibitors (e.g., SKF-525A) may inhibit the development of toxic effects on the liver. Clinical or animal studies examining the use of such an approach and the possibility of side effects, however, were not located.

2.9 ADEQUACY OF THE DATABASE

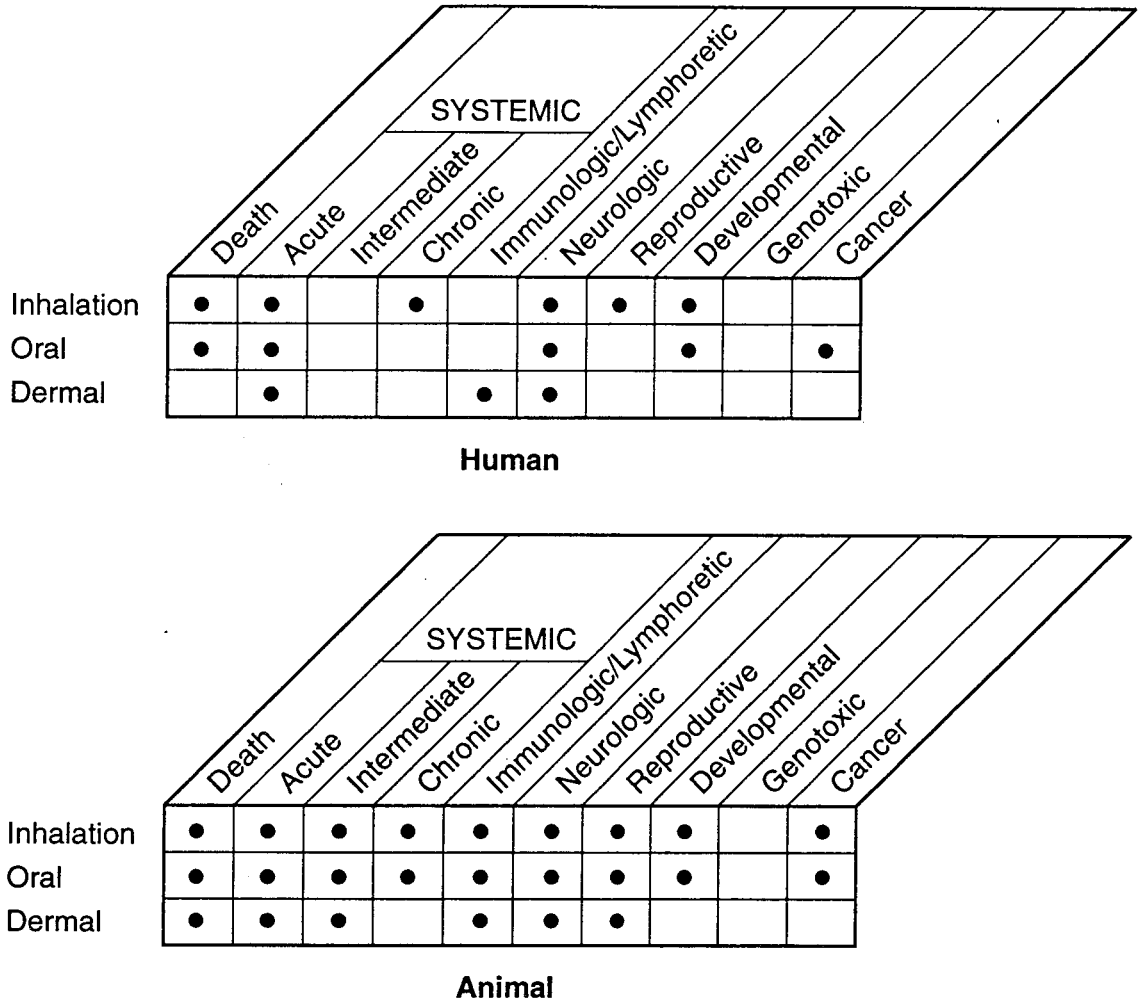
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,1,1-trichloroethane is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,1,1-trichloroethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

2.9.1 Existing Information on Health Effects of 1,1,1-Trichloroethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1,1-trichloroethane are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,1,1-trichloroethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot

FIGURE 2-5. Existing Information on Health Effects of 1,1,1-Trichloroethane



● Existing Studies

does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs." A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Several case studies have documented the lethality of high concentrations of inhaled 1,1,1-trichloroethane. Experimental studies, as well as case reports, have reported on acute systemic and neurological effects. Chronic systemic, neurological, developmental, and reproductive effects have been investigated in epidemiology studies. Health effects caused by other routes of administration have not been as well studied in humans. One case study regarding oral exposure to 1,1,1-trichloroethane reported acute systemic effects and investigated potential neurological effects. Developmental effects and cancer from exposure to drinking water were investigated by epidemiology studies. The effects of dermal exposure are discussed in case reports regarding peripheral neuropathy and dermal sensitization in workers and in controlled studies regarding skin irritation.

As indicated in Figure 2-5, many aspects of the health effects resulting from inhalation, ingestion, and dermal exposure to 1,1,1-trichloroethane have been studied in animals. Except for genotoxicity, each of the end points has been investigated in animals exposed to 1,1,1-trichloroethane by the inhalation and oral routes. Fewer end points have been studied following dermal exposure.

2.9.2 Identification of Data Needs

Acute-Duration Exposure. The primary target organs of 1,1,1-trichloroethane toxicity have been identified from human and animal studies. The central nervous system appears to be the most sensitive target organ after inhalation exposure. Decreased psychomotor performance, altered EEG, ataxia, and anesthesia have been observed in humans after inhalation exposure (Domette and Jones 1960; Gamberale and Hultengren 1973; Mackay et al. 1987; Stewart et al. 1961, 1969, 1975; Torkelson et al. 1958). Cardiovascular effects (decreased blood pressure and arrhythmias) and mild hepatic effects (increased serum enzyme levels, fatty liver, choles.tasis) have also been observed (Domette and Jones 1960; Guberan et al. 1976; Halevy et al. 1980; Hodgson et al. 1989; Krantz et al. 1959; MacDougall et al. 1987; Stewart 1971; Stewart et al. 1961; Travers 1974). Developmental

toxicity studies in rats and rabbits indicated that 1,1,1-trichloroethane can cause mild developmental delays and effects in the offspring at high levels (usually accompanied by significant maternal toxicity) (BRRC 1987a, 1987b; York et al. 1982). Acute oral studies have determined lethal levels in animals and have shown that ingested 1,1,1-trichloroethane produces neurological effects and reduced body weight gain in animals, and perhaps mild liver effects as well (Bruckner 1983; Spencer et al. 1990; Torkelson et al. 1958; Tyson et al. 1983). The only human data on ingested 1,1,1-trichloroethane was a single case report (Stewart and Andrews 1966). The distribution of 1,1,1-trichloroethane to the central nervous system after oral administration has not been investigated, but is likely to be similar to that following inhalation exposure. In an oral study of rats and mice, however, a significant concentration of 1,1,1-trichloroethane or its metabolites was found in the liver, a possible target organ (RTI 1987). Data from dermal studies indicate only that concentrated 1,1,1-trichloroethane is a skin irritant (Duprat et al. 1976; Stewart and Dodd 1964; Torkelson et al. 1958; Wahlberg 1984a, 1984b). Pharmacokinetic data based on dermal exposures are limited; however, 1,1,1-trichloroethane is absorbed following dermal exposure (Fukabori et al. 1977; Stewart and Dodd 1964; Tsuruta 1975). Therefore, the central nervous system and the liver are likely to be target organs after sufficient dermal exposure, although doses required to produce effects would be difficult to predict. Data from inhalation studies in humans were sufficient to derive an acute inhalation MRL based on decreased psychomotor performance (Mackay et al. 1987). An acute oral MRL, was not derived due to lack of adequate data.

Populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane for brief periods. 1,1,1-Trichloroethane is a frequent contaminant of drinking water supplies, although doses of 1,1,1-trichloroethane ingested by persons living near waste sites are generally significantly lower than doses shown experimentally to cause central nervous system depression or cardiac arrhythmias. Nevertheless, valuable information could be gathered from acute oral toxicity studies with neurological and cardiovascular end points. Similarly, acute dermal studies have focused on death and skin irritation, but have not determined the doses that might produce other effects. This information might be useful because dermal exposure to 1,1,1-trichloroethane is common among workers in certain industries, including those who clean up toxic waste sites.

Intermediate-Duration Exposure. No studies were located regarding intermediate-duration exposure to 1,1,1-trichloroethane in humans. Data from animal studies indicate that the primary target organs of 1,1,1-trichloroethane after intermediate-duration inhalation exposure are the central nervous

system and the liver. Behavioral effects, decreased activity, and unconsciousness have been reported in animals (Mattsson et al. 1993; Moser et al. 1985; Torkelson et al. 1958), as have chemical changes indicative of physical damage to the brain (Rosengren et al. 1985). Mild hepatic effects such as increased liver weight and fatty changes also have been reported (Adams et al. 1950; Calhoun et al. 1981; McNutt et al. 1975; Torkelson et al. 1958). Liver necrosis was reported in one study (McNutt et al. 1975). Decreased body weight gain was reported in several studies (Adams et al. 1950; Prendergast et al. 1967). Ingestion studies reported lethality, narcosis, reduced body weight gain, and mild liver effects (Bruckner 1983; NCI 1977). Reproductive and developmental effects also have been investigated following oral exposure (George et al. 1989; Lane et al. 1982; NTP 1988a, 1988b). The existing information was considered insufficient for derivation of intermediate-duration oral MRL. Intermediate-duration dermal exposure studies revealed only mild hepatic effects and skin irritation (Torkelson et al. 1958; Viola et al. 1981). Pharmacokinetic data to help identify potential target organs after dermal exposure were not located.

Inhalation data were sufficient to derive an intermediate MRL based on chemical changes suggesting physical damage in the brain of gerbils (Rosengren et al. 1985). Data were not sufficient to derive an intermediate oral MRL. Intermediate-duration oral and dermal exposure studies that attempt to determine NOAEL and LOAEL values for systemic and other neurological effects would be valuable, because populations near hazardous waste sites might be exposed to 1,1,1-trichloroethane by these routes for intermediate periods.

Chronic-Duration Exposure and Cancer. The information provided in the limited number of chronic-duration exposure studies in humans is insufficient to define threshold effect levels. Chronicduration inhalation and oral studies in animals have not defined threshold effect levels for most end points, although LOAEL values were reported for decreased body weight in rats and mice (Maltoni et al. 1986; NCI 1977; Quast et al. 1988). No studies of chronic-duration dermal exposure in humans or animals were located. Pharmacokinetic studies after acute oral exposure indicate that the liver is a potential target organ; the mild liver effects observed in chronic-duration animal studies are supportive (Quast et al. 1988). Existing pharmacokinetic data, however, are not sufficient to identify other target organs after chronic oral, inhalation, or dermal exposure, even though relatively high exposure levels have been tested.

MRL values were not derived for chronic-duration inhalation exposure studies because target organs could not be identified. Similarly, a chronic oral MRL was not derived due to lack of adequate data. Because populations near hazardous waste sites might be chronically exposed to 1,1,1-trichloroethane, studies that attempt to determine threshold effect levels for inhalation, oral, and dermal exposure would be valuable.

Two-year cancer bioassays have been performed following both inhalation and oral exposure. The results of one oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats (Maltoni et al. 1986). Definite conclusions or implications could not be drawn based on this report, however, since experimental procedures were compromised, only one dose level was used and only a small number of rats responded. Although no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm (Quast et al. 1988), a followup chronic inhalation bioassay incorporating higher doses, an oral bioassay using several dose levels, larger study groups, and use of more than one species would allow more definitive assessment of 1,1,1-trichloroethane's carcinogenic potential.

Genotoxicity. No studies were located regarding the genotoxic potential of 1,1,1-trichloroethane in humans. Existing genotoxicity studies indicate that 1,1,1-trichloroethane may be weakly mutagenic in *Salmonella* (Gocke et al. 198 1; Nestmann et al. 1980, 1984; Simmon et al. 1977) and is able to transform mammalian cells *in* vitro (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985). Numerous tests of other genotoxic effects have mostly been negative; however, only a few of these studies made an effort to prevent loss of 1,1,1-trichloroethane due to volatility. Studies designed to account for this property would allow a more complete assessment of genotoxicity. Valuable information also would be provided by tests of chromosomal aberrations in peripheral lymphocytes from humans known to have been exposed to 1,1,1-trichloroethane.

Reproductive Toxicity. An epidemiology study found no relationship between adverse pregnancy outcomes and occupational exposure of fathers to 1,1,1-trichloroethane during spermatogenesis (Taskinen et al. 1989). Limited information regarding reproductive toxicity in animals was located. A multigeneration reproduction study of rats exposed to 1,1,1-trichloroethane in drinking water found no reproductive effects (Lane et al. 1982). Histological evaluation of reproductive organs and tissues after

inhalation exposure of rats and mice revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). However, testicular degeneration was observed in guinea pigs (Adams et al. 1950). There are no pharmacokinetic data in humans to help evaluate potential reproductive effects. Reproductive function has not been assessed in animals after inhalation or dermal exposure to 1,1,1-trichloroethane; however, toxicokinetic data available do not suggest route-specific target organs. Nevertheless, an inhalation study of reproductive function in animals would be valuable for assessing reproductive toxicity, since that is the predominant route of exposure for humans to 1,1,1-trichloroethane.

Developmental Toxicity. No relationship between maternal exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes (spontaneous abortions/congenital malformations) was found in human epidemiology studies (Deane et al. 1989; Lindbohm et al. 1990; Swan et al. 1989; Taskinen et al. 1989; Windham et al. 1991; Wrensch et al. 1990a, 1990b). Some studies in animals indicate that 1,1,1-trichloroethane is a potential developmental toxicant in quite high doses. Minor skeletal anomalies (delayed ossification and extra ribs in rats and rabbits, respectively, and decreased fetal body weight in rats) have been reported after inhalation exposure of pregnant rats or rabbits during major organogenesis (BRRC 1987a, 1987b; York et al. 1982). These exposures were at concentrations that also produced significant maternal toxicity in two of the studies (BRRC 1987a, 1987b). No neurological effects were reported in the offspring of rats gavaged with 1,1,1-trichloroethane during gestation and lactation (Dow Chemical 1993). A multigeneration developmental study of oral 1,1,1-trichloroethane exposure reported no teratogenic effects in rats (Lane et al. 1982). Although developmental studies by the dermal route are lacking, pharmacokinetic data available do not suggest route-specific target organs. Furthermore, valuable information can be obtained by using the existing physiologically-based pharmacokinetic models once these are validated by comparison with 1,1,1-trichloroethane levels measured over time in different tissues for the different exposure routes.

Immunotoxicity. No studies were located regarding the immunotoxicity of 1,1,1-trichloroethane in humans. Information regarding the lymphoreticular system was limited to reports of spleen congestion in subjects acutely exposed to high levels of 1,1,1-trichloroethane (Gresham and Treip 1983; Stahl et al. 1969). Exposed mice were not more susceptible to bacterial infection than unexposed control mice after a single inhalation exposure to 1,1,1-trichloroethane (Aranyi et al. 1986). Very limited information exists regarding histology and function of tissues of the lymphoreticular system after

1,1,1 -trichloroethane exposure by any route. Histological evaluation of lymphoreticular tissues, including lymph nodes, thymus, and spleen, revealed no lesions attributable to 1,1,1-trichloroethane exposure (Adams et al. 1950; Calhoun et al. 1981; Kjellstrand et al. 1985b; Prendergast et al. 1967; Tdrkelson et al. 1958).

An acute- or intermediate-duration exposure study including a comprehensive evaluation of lymphoid tissues and blood components would provide valuable information regarding potential immunotoxicity.

Neurotoxicity. The central nervous system is apparently the primary target organ of 1,1,1-trichloroethane toxicity. Behavioral effects, altered EEG recordings, ataxia, unconsciousness, and death have been reported in human and animal studies (Albee et al. 1990a, 1990b; Clark and Tinston 1982; DeCeaurriz et al. 1983; Dornette and Jones 1960; Evans and Belster 1993; Gamberale and Hultengren 1973; Gehring 1968; Kelafant et al. 1994; Mackay et al. 1987; Mattsson et al. 1993; Moser and Balster 1985, 1986; Spencer et al. 1990; Stewart et al. 1961, 1969; Torkelson et al. 1958). Neurochemical changes following prolonged inhalation exposure, suggesting morphological damage to the brain, have been reported in gerbils (Rosengren et al. 1985). Respiratory depression appears to cause death in humans and animals. Most studies were conducted by inhalation exposure, but limited data on oral exposure were also available, including a recent study in which no neurological effects were reported in the offspring of rats treated during gestation and lactation (Dow Chemical 1993) (see Developmental Effects). Neurological effects have not been reported after dermal exposure.

Additional in-depth studies of the effects of 1,1,1-trichloroethane on neurological structure and function might provide important information regarding the mechanisms and reversibility of 1,1,1-trichloroethane-induced neurological dysfunction. Studies to follow-up on the reported changes in GFA protein following 1,1,1-trichloroethane exposure may be helpful. Acute-, intermediate-, and chronic-duration exposure studies by the oral route, including comprehensive histological evaluations and nervous system function tests, would provide information regarding the dose-response relationship for this route of exposure. An acute-duration dermal exposure to assess the potential for neurotoxicity by this route would also be useful, although toxicokinetic data available do not suggest route-specific target organs. Populations residing near hazardous waste sites or in occupational settings might be exposed to 1,1,1-trichloroethane. Well-designed and controlled epidemiology studies of these populations may provide useful information on the potential for 1,1,1-trichloroethane at relevant exposure levels to produce neurological disturbances in humans.

Epidemiological and Human Dosimetry Studies. Epidemiology studies have investigated the relationship between long-term exposure to 1,1,1-trichloroethane and systemic, neurological, reproductive, developmental, and cancer effects in humans, but no health effects associated with exposure have been reported. These studies, however, are limited in design and scope and do not provide definitive conclusions regarding the health effects of 1,1,1-trichloroethane exposure. More extensive studies might provide a definitive assessment of the health hazards of chronic 1,1,1-trichloroethane exposure in humans, especially for occupationally exposed populations. If such effects are identified, human dosimetry studies may be able to correlate 1,1,1-trichloroethane levels in human tissues or fluids with chronic health effects. The usefulness of such studies on individuals living near hazardous waste sites is questionable since exposure is relatively low and the half-life of 1,1,1-trichloroethane and its metabolites too short. Acute experimental studies in humans have established inhalation exposure levels associated with acute neurological effects. Subpopulations potentially exposed to 1,1,1-trichloroethane include people residing near hazardous waste sites where the chemical is stored, people who encounter it in the workplace (either in its manufacture or application), and people who use household products that contain it. It should be mentioned, however, that as a result of Title VI of the Clean Air Act, potential human exposure to 1,1,1-trichloroethane is expected to be gradually reduced (see Chapter 5).

Biomarkers of Exposure and Effect

Exposure. Known biomarkers of 1,1,1-trichloroethane exposure include blood, breath, and urine levels of the chemical and its two major metabolites, trichloroethanol and trichloroacetic acid. Metabolism of trichloroethylene and perchloroethylene also produces trichloroethanol and trichloroacetic acid; therefore, these metabolites are not unique to 1,1,1-trichloroethane (Monster 1988). Environmental 1,1,1-trichloroethane levels are significantly correlated with the levels in blood, breath, and urine (Hartwell et al. 1987a; Monster 1986; Wallace et al. 1982, 1984b, 1985, 1987a, 1987b, 1987~). 1,1,1-Trichloroethane is rapidly cleared from the body after exposure (Astrand et al. 1973; Monster et al. 1979; Nolan et al. 1984; Stewart et al. 1961). The two metabolites have a much longer half-life in the body than the parent compound. Therefore, 1,1,1-trichloroethane levels in the blood, breath, and urine may be used as biomarkers only if they are measured during or shortly after exposure. The two metabolites are more useful as biomarkers for a somewhat longer period after exposure. Because 1,1,1-trichloroethane's half-life in the body is short, and because hematological profiles and clinical

chemistry parameters are not usually affected, the further development of biomarkers based on easilyobtained biological fluids may not be useful.

Effect. No specific biomarkers of effect for 1,1,1-trichloroethane were located in the literature. The central nervous system is apparently the most sensitive organ in humans and animals, and neurotoxicity (decreased psychomotor performance, ataxia, and unconsciousness) is observed after short-term high-level exposure. Development of specific biomarkers of effect would facilitate medical surveillance, which could lead to early detection of adverse effects.

Absorption, Distribution, Metabolism, and Excretion. The absorption, metabolism, and elimination of 1,1,1-trichlorokthane have been studied extensively in humans and animals. Distribution has not been as well studied. 1,1,1-Trichloroethane is rapidly and efficiently absorbed by the lung, skin (under conditions to prevent evaporation), and gastrointestinal tract of humans and animals (Astrand et al. 1973; Fukabori et al. 1977; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Stewart and Andrews 1966; Stewart and Dodd 1964; Tsuruta 1975). As duration of inhalation exposure increases in humans and animals, the percentage net absorption decreases, because steady-state levels are approached in the blood and tissues, and 1,1,1-trichloroethane is metabolized at a low rate. A study with humans equipped with respirators indicated that, during exposure to 1,1,1-trichloroethane vapors in the atmosphere, absorbed doses from inhaled 1,1,1-trichloroethane are much larger than doses from dermal absorption (Riihimaki and Pfaffli 1978). Animal studies demonstrated that, once absorbed, 1,1,1-trichloroethane is distributed by the blood to tissues and organs throughout the body, including developing fetuses, with preferential distribution to fatty tissues (Holmberg et al. 1977; Schumann et al. 1982a; Takahara 1986b). Human data regarding the compound's distribution are limited to the observation that detectable levels were found in subcutaneous fat, kidney fat, liver, lung, and muscle in 30 autopsy cases (Alles et al. 1988). The predominant pathway of 1,1,1-trichloroethane elimination by humans and animals, regardless of exposure route, is exhalation of the unchanged compound (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Reitz et al. 1988; RTI 1987; Schumann et al. 1982a, 1982b). When exposure ceases, the compound rapidly clears from the body. Only trace amounts of the compound remained in animal tissues within days of short-term exposure. Further studies in humans regarding extent and rates of absorption and elimination with dermal exposure to aqueous 1,1,1-trichloroethane solutions or suspensions under conditions allowing evaporation from the skin may provide useful information on dermal contact with contaminated water.

Experiments with animals and humans have demonstrated that only small fractions of absorbed 1,1,1-trichloroethane doses (<10%) are metabolized, regardless of the exposure route (Mitoma et al. 1985; Monster et al. 1979; Nolan et al. 1984; Schumann et al. 1982a, 1982b). 1,1,1-Trichloroethane is metabolized oxidatively to trichloroethanol and trichloroacetic acid by a concentration-dependent, saturable process that appears to involve the cytochrome P-450 mixed-function oxidase system. These metabolites have been detected in urine excreted from exposed humans and animals; other minor metabolites (CO_2 and acetylene, the latter formed by the reductive dechlorination of 1,1,1-trichloroethane under conditions of low oxygen supply) are eliminated in expired air.

The hepatotoxicity of 1,1,1-trichloroethane is quite low compared to other chlorinated hydrocarbons, including 1,1,1-trichloroethane. The relatively low toxicity of 1,1,1-trichloroethane may be due to its relatively low metabolism rate, since the more hepatotoxic halocarbons are extensively metabolized. Whether the mild effects of repeated 1,1,1-trichloroethane exposure are evoked by the parent compound or the limited quantities of metabolites produced is not known, however. The available data indicate that the acute effects on the central nervous and the cardiovascular systems are caused by 1,1,1-trichloroethane and not its metabohtes. The interference of 1,1,1-trichloroethane with membrane mediated processes, due to lipophilicity, may be responsible for the acute effects on these systems; several cellular and biochemical processes appear to be affected by 1,1,1-trichloroethane.

Comparative Toxicokinetics. The toxicokinetic pattern of 1,1,1-trichloroethane is qualitatively similar in humans, rats, and mice. There are major quantitative differences, however, including a higher blood:air partition coefficient, higher respiratory and circulatory rates, and increased rate of metabolism in mice. This comparison has led to a suggestion that rats may be a better model for humans than mice. Physiologically-based pharmacokinetic models have been developed to describe the kinetic behavior of 1,1,1-trichloroethane in mice, rats, and humans; these models have been used to make interspecies and interroute extrapolations in estimating 1,1,1-trichloroethane exposure levels in humans that will produce (or not produce) toxic effects (Bogen and Hall 1989; Dallas et al. 1989; Leung 1992; Nolan et al. 1984; Reitz et al. 1988; USAF 1990). Further research verifying the metabolic constants and other input parameters (partition coefficients, tissue values and blood flows, cardiac output, and respiratory volumes) used in these models might improve the accuracy and utility of the models in interspecies extrapolations.

Methods for Reducing Toxic Effects. Suggested methods to treat the effects of acute exposure to 1,1,1-trichloroethane and other halogenated hydrocarbons are generally supportive and rely on the body's ability to eliminate rapidly 1,1,1-trichloroethane and its metabolites. Animal studies indicate that intravenous injection or infusion of calcium gluconate or phenylephrine are protective against acute blood pressure reduction caused by exposure to 1,1,1-trichloroethane (Herd et al. 1974). Further animal testing is needed to assess whether these compounds might be used to resuscitate individuals exposed to high concentrations of 1,1,1-trichloroethane.

2.9.3 Ongoing Studies

J.L. Poyer of the Oklahoma Medical Research Foundation is examining the correlation between hepatic free radical formation (determined with electron spin resonance techniques) and liver injury (assessed by electron microscopy and serum sorbitol dehydrogenase) in rats treated with a series of halogenated hydrocarbons including 1,1,1-trichloroethane (CRISP 1992). Investigations will include determining the capacities of free radical quenching and trapping agents to prevent liver injury.

A. Braun is conducting a 13-week dietary study of 1,1,1-trichloroethane in rats and mice (CRISP Database 1992). The study will include hematological and clinical chemistry examinations, sperm morphology and vaginal cytology examinations, and urinary metabolite analysis.

Dr. R. Balster and his colleagues at the Medical College of Virginia will examine the effects of 1,1,1-trichloroethane in mice relative to those of ethanol and other drugs of abuse (FEDRIP 1994). Dr. Balster proposes to develop new behavioral test procedures to study inhalant-self administration, place preference conditioning, effects on motor activity, multiple-schedule performance; and punished responding.

Dr. J. Bruckner and his colleagues at the University of Georgia are collaborating with EPA scientists to develop more accurate PBPK models for prediction of time integrals of target organ exposure to 1,1,1-trichloroethane.